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No. 07- 07-838

IN THE

Supreme Court of the United States

ALPHAPHARM PTY., LTD. and GENPHARM, INC.,

Petitioners,

v.

TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

PETITION FOR A WRIT OF CERTIORARI

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QUESTION PRESENTED

In *KSR International Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1739 (2007), this Court reaffirmed its earlier precedents governing whether an invention is obvious to one skilled in the art and therefore unpatentable. Before this Court's ruling in *KSR*, courts would seek in the prior art proof of a "teaching, suggestion, or motivation" ("TSM") to combine prior-art teachings in order to conclude a patent was obvious. Observing that the TSM test was based neither in Supreme Court precedent nor statute (35 U.S.C. § 103(a)), this Court unanimously reversed, holding that the obviousness analysis was "flexible" and need not "seek out precise teachings directed to the specific subject matter of the challenged claim." *Id.* at 1739, 1741. Obviousness depends instead on the "objective reach" of the claim. *Id.* at 1742. "If the claim extends to what is obvious, it is invalid under § 103." *Id.*

In this case—despite this Court's holding in *KSR*—the Federal Circuit rigidly applied the TSM test to hold that obvious compounds were not obvious. The patent at issue, U.S. Patent No. 4,687,777 ("the '777 patent"), claimed chemical compounds used to treat diabetes. These compounds were so closely related in structure to the closest prior art—a highly effective anti-diabetic compound repeatedly touted in the prior art—as to be presumed obvious under patent law. Petitioners demonstrated at trial that all of the compounds claimed in the '777 patent could have been made with routine modifications to that compound. But the Federal Circuit rejected an analysis based on the "objective reach of the claim" and instead required a showing that "***the prior***

art would have suggested making the specific molecular modifications" to achieve the claimed invention. *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007) (emphasis added). Does the standard that the Federal Circuit applied materially conflict with this Court's holding in *KSR*?

PARTIES TO THE PROCEEDING

This case arises from two separate challenges to the validity and enforceability of the '777 patent arising under the Hatch-Waxman Amendments to the Federal Food, Drug, & Cosmetic Act (collectively "the Hatch-Waxman Act"). *See* 21 U.S.C. § 355 et seq. The Hatch-Waxman Act allows generic pharmaceutical companies, such as Petitioners Alphapharm Pty., Ltd. and Genpharm Inc. (collectively "Alphapharm"), to certify their intent to seek marketing approval of a brand-name drug before patent expiry, so long as they certify that any patent listed by the brand-name pharmaceutical company as covering that drug, or a method of its use, is not infringed, invalid, or unenforceable. In return, the Hatch-Waxman Act allows the patent holder to file an infringement proceeding against the generic pharmaceutical company seeking such marketing approval.

Alphapharm certified that the compounds claimed in the '777 patent were obvious, and thus invalid, over the prior art. Mylan Laboratories, Inc., Mylan Pharmaceuticals, Inc., and UDL Laboratories, Inc. (collectively, "Mylan") also certified that the '777 patent was obvious. Respondents Takeda Chemical Industries, Ltd. and Takeda Pharmaceuticals North America, Inc. (collectively "Takeda") sued Alphapharm and Mylan in the Southern District of New York for infringement of the '777 patent. While the case was pending, Mylan also challenged the '777 patent as unenforceable as a result of Takeda's inequitable conduct before the Patent Office.

The case was tried in January 2006 before the bench. The district court ruled that the '777 patent was valid and enforceable. Alphapharm and Mylan appealed, and the Federal Circuit affirmed in separate decisions.

CORPORATE DISCLOSURE STATEMENT

The parent corporation and/or publicly held company that owns 10% or more of the stock of Petitioners Alphapharm Pty., Ltd. and Genpharm Inc. is Mylan, Inc. (Since the trial and appeal, Mylan Inc. acquired Alphapharm Pty., Ltd. and Genpharm Inc.)

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Alphapharm respectfully requests that this Court grant its petition for a writ of certiorari, reverse the judgment of the Federal Circuit, and enter judgment that claims 1, 2, and 5 of the '777 patent are obvious as a matter of law.

OPINIONS BELOW

The Federal Circuit's opinion is reported at *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007), and is set forth in the appendix at A1-30. The opinion of the United States District Court for the Southern District of New York is reported at *Takeda Chemical Industries, Ltd. v. Alphapharm Pty., Ltd.*, 417 F. Supp. 2d 341 (S.D.N.Y. 2006), and is set forth at A31-161.

JURISDICTION

The Federal Circuit entered judgment on June 28, 2007. (A168-69.) The Federal Circuit denied a combined petition for panel rehearing and rehearing en banc on September 27, 2007. (A170-71.) This Court has jurisdiction under 28 U.S.C. § 1254(1).

STATUTORY PROVISIONS

This case relates to the obviousness statute set forth in 35 U.S.C. § 103(a):

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art

> are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

STATEMENT OF THE CASE

This petition raises a question of real legal significance: what is the proper standard to determine the structural obviousness of a chemical compound? The answer to this question affects every issued U.S. patent claiming chemical compounds, every pending application claiming chemical compounds, and every litigation where a claim reciting a chemical compound is at issue.

In April 2007, this Court rejected strict application of the Federal Circuit's TSM test because it was supported neither by the obviousness statute nor Supreme Court precedent. Section 103 requires that courts examine the differences between the subject matter sought to be patented and the prior art and make specific factual findings on the significance of these differences to the skilled artisan. *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 15-17 (1966). If what is claimed is simply the product of routine innovation over the prior art, it is obvious under § 103. *KSR*, 127 S. Ct. at 1741. The closest prior art is naturally compared to the claimed invention, as the skilled artisan is presumed to know all of the pertinent prior art. *See, e.g., Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1360-61 (Fed. Cir. 2007) (proceeding to find patent invalid as obvious from

the starting point of the closest prior art); *In re Huston*, 308 F.3d 1267, 1278 (Fed. Cir. 2002) (same). But here, the Federal Circuit reversed this analysis, and required that Alphapharm point to prior art that particularly motivated the skilled artisan to first select the closest prior-art compound, and then modify it in exactly the manner claimed. This was error and it provides ample basis for the Court to grant certiorari.

But the Court should grant certiorari for another reason. In applying the TSM test here, the Federal Circuit reasoned that some side effects from the closest prior-art compound would teach the skilled person away from making any modifications to it. But as Alphapharm demonstrated at trial—and as this Court recognized in *KSR*—this is precisely why the skilled artisan would make such changes. "[T]he claimed subject matter may involve more than the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement." *KSR*, 127 S. Ct. at 1740. Pharmaceuticals are expected to have effects in the body other than their indicated use. Reducing a side-effect profile is precisely the reason that skilled artisans make conservative substitutions in chemical compounds. (SA111.)

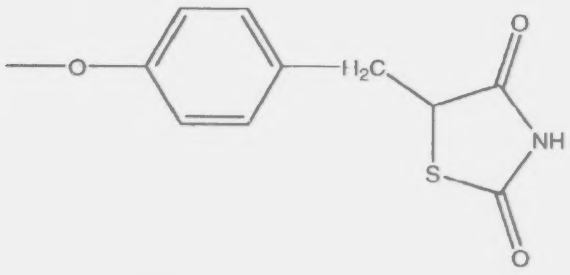
I. The Claimed Chemical Compounds and the Prior Art

This case concerns the chemical compound pioglitazone, which is used to treat Type 2 diabetes, and other related compounds claimed in the '777 patent. Type 2 diabetes is a condition where the body fails to utilize its insulin effectively, thereby resulting in unhealthy

blood sugar levels. In August 1987, the Patent Office issued the '777 patent. Takeda markets pioglitazone in the United States as the drug Actos®.

A. The Principal Antidiabetic Structure

The compounds claimed in the '777 patent are called thiazolidinediones ("TZDs"), which have been known for their antidiabetic properties since at least 1981 when Takeda's own U.S. Patent No. 4,287,200 ("the '200 patent") issued. The '200 patent disclosed a large number of TZD compounds, and touted their antidiabetic effects and "low toxicity" over the prior art. (SA28-37.) Shortly thereafter, Takeda disclosed that the antidiabetic properties of these compounds are related to the right-hand portion (or moiety) of the compound[1] as depicted below:



(SA54.) Takeda's work thereafter consisted of attaching various chemical structures to the left-hand side of the molecule to either minimize toxicity or optimize antidiabetic efficacy. (SA45-65.) Many of these structures are covered in the claims of the '200 patent.

---

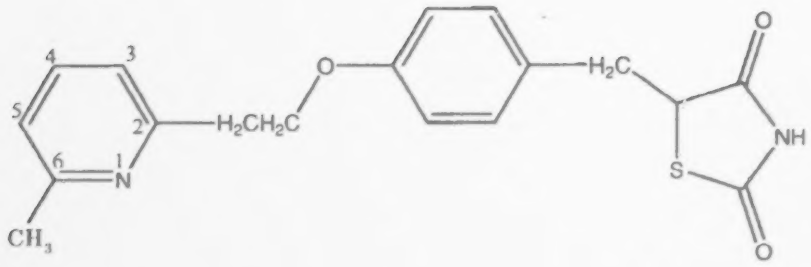
1. The pentagonal structure at the right of the figure depicted is known as a thiazolidinedione.

B. Compound b

In 1982, Takeda disclosed the efficacy results from its research into the structure-activity relationships on the left-hand side of TZDs in the prior-art reference, T. Sohda et al., "Studies in Antidiabetic Agents. II Synthesis of 5-4-(1-Methylcyclohexylmethoxy)-benzyl]thiazolidine-2,4,dione (ADD-3878) and Its Derivatives." (hereinafter "Sohda II"). (SA45-65.) By the time the Sohda II reference was published, the most effective antidiabetic TZD compound in the prior art was set forth in Sohda II as compound 58 but labeled in this case as "compound b." (This compound was compared against pioglitazone and other compounds in a chart in the '777 patent, listing it as "compound b." The same name will apply here.) When prosecuting the '200 patent, for example, Takeda submitted an inventor declaration identifying the best nine compounds to overcome certain prior art cited by the examiner. (SA43.) Compound b's efficacy scores were higher than any other compound. (SA43.) No compound in Sohda II scored higher. (SA48-53.) Compound b is the closest prior-art compound to those claimed in the '777 patent. (A13.)

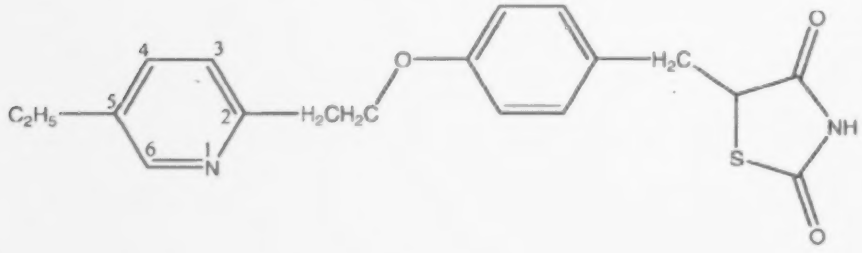
The left-hand side of compound b has a methyl (CH_3) group at what is called the "6 position" in organic chemistry parlance.

Compound b



The claimed compound, pioglitazone, is closely-related in structure to compound b:

Pioglitazone



Thus, compound b and pioglitazone differ only in the location and length of the group attached to the left-most ring known as a pyridyl. The structural similarity between compound b and the compounds claimed in the '777 patent could not be closer. The '777 patent includes claims drawn to an ethyl substituent at the 6-position—the same position as compound b. Extension by one carbon atom is the only difference between the claimed compounds and compound b. Pioglitazone is covered by claim 2 of the '777 patent, where the C_2H_5 group appears

at the 5 position. All of the compounds have the same antidiabetic properties, namely, lowering of serum glucose and triglycerides. Indeed, as noted by the Federal Circuit, the parties agreed that compound b was the closest prior art. (A13.)

C. Reason to Modify Compound b

The job of a medicinal chemist is to modify a given chemical compound to either improve its efficacy or decrease its toxicity. (SA111, ¶28.) Alphapharm presented evidence at trial demonstrating that compound b was an ideal candidate for routine tweaking based on Takeda's disclosures in the '200 patent (including its file history) and Sohda II. (SA111-13.) While compound b had the best efficacy of all the TZD compounds Takeda disclosed, it was not perfect. Sohda II remarked that the compound caused "considerable increases in body weight and brown fat weight." (SA54.) While brown fat weight was not a concern that affected human beings, body weight was. (SA84, pp. 910:17–911:9.) Alphapharm presented evidence at trial demonstrating that the medicinal chemist faced with a compound with superb efficacy but some side effects would make conservative changes to the compound, by substituting the 1-carbon methyl group with a 2-carbon ethyl group and moving that ethyl group to other potential places on the left-most ring of the compound. (SA111-12.) Adding a carbon atom to a group is called homologation. (SA111-12.) Moving a group around a ring is called ring-walking. (SA111-12.) Even Takeda's expert witnesses agreed that making such changes were well-known in medicinal chemistry at the time. (SA78-79;

SA88-89.) Indeed, Takeda taught the skilled artisan as much when it later sought patent protection for compound b, before the '777 patent was applied for. In that patent, U.S. Patent No. 4,444,779 ("the '779 patent"), Takeda disclosed that the constituent groups that the skilled artisan should use on available portions of the left-most pyridyl ring depicted above included "methyl, ***ethyl***, etc." (SA10, col. 2; ll. 43-45) (emphasis added.)

Takeda also admitted while prosecuting the '779 patent application that the earlier "problem" with compound b highlighted in Sohda II was no deterrent to patentability. Takeda argued to the examiner that compound b had become "especially" "important." (SA24.) Takeda also argued to the examiner that the class of substituted pyridyls was narrow, well-defined, and would have a predictable biological effect:

> the substituents in this case, ***actually cover a relatively narrow and well-defined group of constituents.*** Moreover, there should be no reason in the instant case for the Examiner to doubt that ***the claimed compounds having the specified substituent would function as a hypolipidemic and hypyglycemic (sic) agent as specified*** in the instant disclosure.

(SA26–27) (emphasis added.)

II. The District Court Decision

After a 13-day bench trial, the district court held the '777 patent valid. (A32-33.) But the district court's analysis was based on a flawed perception of the law of chemical obviousness:

> In the case of a chemical compound, a prima facie case of obviousness exists where there is a "structural similarity between claimed and prior art subject matter" ***and "the prior art gives reason or motivation to make the claimed compositions."*** *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343 (Fed. Cir. 2000) (citation omitted).
>
> "[O]bviousness may render a claimed invention invalid where the ***record contains a suggestion or motivation to modify the prior art*** teaching to obtain the claimed invention." *Beckson*, 292 F.3d at 727. Thus, an invention is prima facie obvious where the prior art would imbue one of ordinary skill in the art with a "reasonable expectation of success" ***in achieving the goals that the inventor sought to accomplish*** by transforming a compound in the prior art into the structurally similar claimed invention. *Yamanouchi*, 231 F.3d at 1343 (citation omitted).
>
> * * *
>
> Where the creation of a chemical compound requires the chemist to pursue several steps in manipulating a compound revealed in the

> prior art, ***the patent challenger must show that one of ordinary skill in the art would have had sufficient motivation to take each of those steps.*** *Id.* at 1344-45.

(A93-94) (emphasis added.)

Based on its view of the law—more than one year before this Court's decision in *KSR*—the district court required Alphapharm to prove both a particular motivation to select the closest prior-art compound and a particular motivation to combine the prior art to obtain the claimed pioglitazone—or one of the ethyl-substituted TZDs. (A96.) Nothing in § 103 or this Court's precedents requires proof of either.

The district court further held that "the prior art did not disclose or suggest either the pioglitazone molecule itself or how to make it." (A96.) And the district court held that one skilled in the art would not have "chosen compound b as a lead compound," finding that Alphapharm failed to prove that a skilled artisan would "have had sufficient motivation" to make the simple substitutions Takeda itself taught in the '779 prior-art patent. (A96.)

In analyzing the prior art, the district court determined that one of skill in the art would not have been motivated to select compound b as a lead compound—the undisputed closest prior art—because Sohda II "taught away" from compound b owing to the side effects of brown fat and weight gain. (A104-08.)

Alphapharm appealed the district court's validity ruling to the Federal Circuit.

III. The Federal Circuit's Affirmance

The Federal Circuit affirmed. Although it recognized that *KSR* clarified the law of obviousness, the Federal Circuit required: (1) proof that the skilled person would have found the specific reason in the prior art for selecting the closest prior art as a lead compound; and (2) proof that the ***"prior art would have suggested making the specific molecular modifications"*** to achieve the claimed compound in exactly the manner claimed. (A11) (emphasis added.) In applying this test here, the Federal Circuit held that "the closest prior art compound (compound b, the six-methyl) exhibited negative properties that would have directed one of ordinary skill away from that compound." (A18.)

Alphapharm moved for a petition for rehearing and rehearing en banc but the Federal Circuit denied those petitions. (A170-71.)

REASONS FOR GRANTING THE PETITION

I. The Federal Circuit's Affirmance Conflicts with *KSR*'s Flexible Approach Because it Rigidly Applied the "Teaching, Suggestion, or Motivation" Test

The law presumes that structurally similar compounds —especially when used for the same purpose in the prior art—are prima facie obvious. This presumption arises because the law recognizes that structurally similar compounds are presumed to have similar properties. *In re Grabiak*, 769 F.2d 729, 731 (Fed. Cir. 1985) ("when chemical compounds have 'very close' structural similarities and similar utilities, ***without more*** a *prima facie* case may be made.") (bold emphasis added). This comports with this Court's "common sense" approach stated in *KSR*. *KSR*, 127 S. Ct. at 1742.

"[S]tructural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness." *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc); *see also In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995). The prior art repeatedly taught that substituted TZDs had antidiabetic properties and low toxicity. But the Federal Circuit additionally required particular explicit motivation in the prior art to both select the closest prior art and to modify it in specific ways. Such a test is inconsistent with *KSR*, as it would impose a particular TSM requirement in every chemical obviousness case. This rigid application is just the type of analysis the Supreme Court rejected in *KSR*.

A. This Rigid Chemical Obviousness Test Requires a New and Onerous Requirement for Obviousness—Motivation to Find the Closest Prior Art

In *KSR*, this Court ruled that the TSM test while capturing a "helpful insight," may at times be inconsistent with the obviousness inquiry. *KSR*, 127 S. Ct. at 1741. Section 103 of Title 35 does not focus on how the prior art would motivate the skilled artisan to reach the invention. *Id.* Rather, for obviousness,

> [w]hat matters is the ***objective reach of the claim***. If the claim extends to what is obvious, it is invalid under § 103. One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims.

Id. at 1742 (emphasis added).

The obviousness analysis starts—not with the prior art and what motivated the skilled person—but with the claims. Courts must examine what is claimed and then determine whether the person of ordinary skill in the art could attain the invention using ***any*** predictable means from the closest prior art. *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986) (noting that the skilled artisan is presumed to be aware of ***all*** prior art.) For example, in *KSR*, the patent at issue [Engelgau] covered adjustable automobile pedals with an electronic sensor to detect the position of the pedal and transmit that position to a computer-controlled throttle. *KSR*, 127 S. Ct. at 1736-37. The Asano patent was the closest prior art, and

covered each element of the Engelgau claims but not the use of a sensor. *Id.* at 1738. This Court did not analyze why the skilled person would select Asano from the prior art. Instead, the analysis focused on whether the Asano design "provided an obvious example of an adjustable pedal with a fixed pivot point." *Id.* at 1742. It was of no importance that Asano was designed to solve another problem that might deter the skilled person. As this Court acknowledged, "a person of ordinary skill is also a person of ordinary creativity, not an automaton." *Id.*

Here, the Federal Circuit failed to perform an analysis based on the objective reach of the claim. Rather, Alphapharm was required to prove in the first instance why a person of skill would select compound b as the best compound from the prior-art compounds available. (A13-14.) This departure from *KSR*'s holding is evident throughout the district court's opinion (adding bold italics):

> The prior art did not ***disclose*** or suggest either the pioglitazone molecule itself or how to make it. (A96);
>
> To begin with, the evidence is overwhelming that one skilled in the art would not have, based on the prior art, chosen compound (b) as ***a lead compound***. (A96);
>
> The discussion that follows examines each of the Graham factors, ***paying particular attention to the identification of a lead compound***, the motivation to alter that compound, and unexpected results. (A97);

and the Federal Circuit's opinion (adding bold italics):

> By "lead compound," we understand Alphapharm to refer to a compound in the prior art that would be ***most promising to modify***. . . . (A13);
>
> The court, however, found nothing in the '200 patent, . . . to suggest to one of ordinary skill in the art that those nine compounds . . . were the ***best performing compounds*** as antidiabetics. . . . (A14.)

Curiously, the Federal Circuit's decision to require specific proof that the skilled person would select compound b as the best compound in the prior art was contrary to that court's own precedent. For example, in *In re Fulton*, the court held that the prior art need not teach that a particular combination is "preferred" or "optimal" to be obvious. 391 F.3d 1195, 1201-02 (Fed. Cir. 2004). Alphapharm never had to prove that compound b was the best compound or that no other routes were available. *Id.* at 1202. Rather, "'the question is whether there is something in the prior art as a whole to suggest the *desirability*, and thus the obviousness, of making the combination.'" *In re Beattie*, 974 F.2d 1309, 1311 (Fed. Cir. 1992) (emphasis in original). The prior art here both showed methyl and ethyl substituted-TZDs were promising. The '779 patent focused specifically on methyl ***and ethyl*** substitutions on the left-hand pyridyl ring of TZD compounds. (SA10 at col. 2, ll. 40-45.) Indeed, Takeda represented to the Patent Office that one such example, compound b, had become "especially" "important." (SA24.)

Nothing in the science of medicinal chemistry or any of the chemical arts supported the Federal Circuit's requirement that a lead compound be the "most promising to modify." (A13.) A lead compound need not be the "leading" or the best. Rather, a lead compound is one that has desired activity but some deficits. (SA111.)

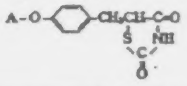
There can be no question of harm here. Given the departure from the *KSR* analysis, the Federal Circuit (and the district court) could never reach the threshold inquiry required. "A court must ask whether the improvement [over the closest prior art] is more than the predictable use of prior art elements according to their established functions." *KSR*, 127 S. Ct. at 1740. Under that standard, the compounds claimed in the '777 patent are clearly obvious.

1. The Proper Analysis Under *KSR* Demonstrates that the Claims of the '777 Patent Would Have Been Obvious

A compound is obvious where "the claimed subject matter [involves] the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement." *KSR*, 127 S. Ct. at 1740. A patent challenger need only point to the availability of a compound in the prior art that gave the skilled artisan "an apparent reason to combine the known elements in the fashion claimed." *Id.* at 1741. Here, the prior art repeatedly promoted substituted TZDs, including methyl and ethyl substitutions, and thus provided a reason to modify compound b with homologation and ring-walking to arrive at the claimed pioglitazone.

Alphapharm demonstrated the reason to modify at trial. One structural difference separates the ethyl genus claimed in the '777 patent and compound b—a C_2H_5 rather than a CH_3 at the 6-position on the ring. Two structural differences separate pioglitazone and compound b. Takeda added a CH_2 group to the methyl (CH_3) on the pyridyl ring of compound b and moved the resulting ethyl one position over on the ring—from the 6 position to the 5 position. Because compound b was already known as the most efficacious antidiabetic compound in the prior art—but with some side effects—the skilled person had a reason to make these minor changes. (SA43.) In the following table excerpt, compound b is referred to as compound 58. The data in Takeda's own Sohda II reference demonstrated that the triglyceride-lowering potency doubled when a methyl substituent was added to the unsubstituted pyridyl ring (shown as compound 57) to obtain compound 58. In the table, the higher the score, the greater the potency (A48-49):

TABLE IV. Physical and Biological Properties of Thiazolidine-2,4-dione Derivatives



No.	A	Method[a]	Yield[b] (%)	mp (°C)	Recrystn. solvent[c]	Formula[d]	Hypoglycemic activity[e]	Plasma triglyceride-lowering activity[f]
56		B	55.6	183–184	C–M	$C_{16}H_{16}N_2O_3S$	3	3
57		B	55.4	209–210	DMF–W	$C_{17}H_{16}N_2O_3S$	3	2
58		B	42.7	103–104	EA–H	$C_{18}H_{18}N_2O_3S \cdot 1/2H_2O$	3	4
59		B	51.6	175–176	C–M	$C_{17}H_{16}N_2O_3S$	[illegible]	[illegible]
60		B	77.6	176–177	C–M	[illegible]	3	2

Addition of a single CH_3 group doubled lipid-lowering activity from 2 to 4.

(SA51.) The skilled artisan would have understood that any attempt to maintain the activity of compound 58 (i.e., compound b) would require ameliorating the compound's side effects by making conservative changes to the pyridyl ring, substituting with methyls and ethyls at the four available places on the ring (i.e., the 3, 4, 5, and 6 positions). (SA112.)

Moreover, Takeda had provided in the prior art the very instruction for making these changes. Takeda had sought coverage of substituted pyridyls (including pioglitazone) in its prior-art '779 patent. There, Takeda taught the skilled artisan homologation and ring-walking on the pyridyl ring with ethyl substituents: "***As examples of such substituents may be mentioned lower alkyls (e.g. methyl, ethyl, etc.)***. . . ." (SA10 at col. 2, ll. 44-45) (emphasis added.)

All of the compounds could have been achieved by applying conventional techniques in medicinal chemistry to improve the profile of known chemical compounds, including homologation and ring-walking. Applying homologation to improve the profile of the prior-art compound b would have invalidated claims 1 and 5 of the '777 patent. Applying the well-known technique of ring-walking would have invalidated claim 2, the claim drawn to pioglitazone. (SA113.) As this Court observed in *KSR*, "if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill." *KSR*, 127 S. Ct. at 1740. There can be no argument that homologation and ring-walking were beyond the purview of the skilled artisan.

Takeda's reasoning in the '779 patent—that substituted TZDs including methyl and ethyl substitutions are promising antidiabetic compounds, and that compound b is especially so—gives the skilled artisan the reason to synthesize and test the compounds claimed in the '777 patent, just as *KSR* urges.

2. Takeda Admitted that Adding Substituents to the Pyridyl Ring Would Have Resulted in Compounds with the Same Antidiabetic Effect

A design need existed to solve a problem—minor side effects associated with compound b. The number of possible solutions, based on Takeda's admissions, was quite small. The district court found, and the Federal Circuit affirmed, that "thousands" of possibilities existed. (A107; A19-20.) But methyl and ethyl substituents can exist at only four locations on the pyridyl ring in question resulting in seven variants (excluding compound b because it is prior art). (SA114.) Under *KSR*, the only remaining inquiry is whether the solutions are predictable. Here, Takeda itself admitted that predictability in the '779 patent prosecution history: "the substituents in this case, actually cover a relatively narrow and well-defined group of constituents . . . [that] would function as a hypolipidemic and hypyglycemic (sic) agent as specified in the instant disclosure." (SA26-27.) The skilled person was thus taught that making such conservative changes would not affect the compound's antidiabetic use. *See also McNeil-PPC, Inc. v. Perrigo Co.*, — F. Supp. 2d —, No. 05-1321, 2007 WL 1933931, at *8 (S.D.N.Y. July 7, 2007) (finding drug patent obvious in light of, among other things, the inventor's admissions).

The Federal Circuit also affirmed the nonobviousness of the other claims in the '777 patent reciting ethyl-substituted pyridines in positions 3, 4, and 6. (A28.) But Judge Dyk, in his concurrence, found that claims 1 and 5, which also covered pioglitazone, were so broad as to be "likely invalid." (A28.) Nowhere in the '777 patent is there any evidence that these other ethyl-substituted compounds would even be active. The table evidencing activity for these compounds is based entirely on activity in pioglitazone. (SA5.) Takeda clearly relied on the common sense of the skilled artisan, who was expected to understand that these other ethylated compounds had predictable activity, i.e., a "broad safety margin" similar to pioglitazone's. (SA3, col. 1, l. 37.)

Under *KSR*, no compound can receive patent protection where it represents nothing more than "the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement." *KSR*, 127 S. Ct. at 1740. Alphapharm amply demonstrated the obviousness of the claimed compounds under *KSR*. Only by ignoring the proper inquiry—and requiring as an additional prerequisite the specific motivation for the skilled person to select the closest prior art and receive particular instructions on modification—was the panel able to affirm nonobviousness.

B. The Prior Art Did Not Teach Away from the Claimed Invention

In affirming the district court, the Federal Circuit agreed that Sohda II's statements about compound b's brown-fat and weight-gain effects "taught away" from compound b. (A17.) But where the claimed invention does not exhibit "markedly superior" properties over the prior art, the claim is obvious. *In re Coes*, 173 F.2d 1012, 1014 (C.C.P.A. 1949) (invalidating claims to adjacent homologues in the prior art).

Here, by overemphasizing the side effects of compound b noted in Sohda II, the district court turned a deaf ear both to Takeda's later representations in the '779 patent to use methyl and ethyl groups on the left-most pyridyl ring, and the overwhelming similarities in both structure and properties between compound b and pioglitazone. (A106-07.) For instance, Takeda obtained the '779 patent covering substituted pyridyls—and compound b in particular—based on the assertion that compound b had become "especially" "important." (SA24.) Takeda vitiated any argument that compound b was "unlikely to be productive of the result sought"—the test for teaching away—when Takeda obtained the '779 patent and drew a specific claim to that compound and other lower-alkyl substituted TZDs. (SA19.) *See Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006).

In any event, Takeda's expert witness and fact witnesses from its development partner, Upjohn, admitted that any concerns about brown fat in Sohda II were speculative when it comes to human beings, and

weight gain was a sign that the compound was working. (SA71; SA129; SA84.) These admissions demonstrate that the comments in Sohda II on compound b's side-effect profile would not have precluded the skilled artisan from selecting that compound—even if Takeda had chosen not to patent this "especially" "important" compound. (SA24.)

In *KSR*, the Supreme Court cautioned lower courts against making such errors. 127 S. Ct. at 1740. "Rigid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it." *Id.* at 1742-43. "[I]n many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle." *Id.* at 1742. The skilled artisan piecing together Takeda's later representations would, at the very least, have reason to create the lower-alkyl (e.g., methyl and ethyl) substituted TZDs Takeda expressly taught in the '779 patent. And the '779 patent demonstrated that Takeda had singled out compound b as an especially important compound. Indeed, compound b was a lead compound for Takeda during this time frame. (SA91) (noting that pioglitazone, labeled ADD-4833, was a peripheral compound of compound b, labeled ADD-3959.)

Eli Lilly & Co. v. Zenith Goldline Pharmaceuticals, Inc., 471 F.3d 1369, 1378 (Fed. Cir. 2006), *cert. denied*, 128 S. Ct. 146 (2007), relied upon below by Takeda, is not on point. *Eli Lilly* concerned the validity of Eli Lilly's patent directed to olanzapine—a compound used to treat schizophrenia. *Id.* at 1373. The challenger alleged that olanzapine was obvious over its closest structural

relative, ethyl-olanzapine. *Id.* at 1377-78. Ethyl-olanzapine and olanzapine are homologs of each other, as here. *Id.* at 1379.

But the similarity between *Eli Lilly* and this case stops at structure. The closest prior art in *Eli Lilly* was "less active" as an antipsychotic drug than olanzapine. *Id.* at 1379. In *Eli Lilly*, ***all*** of the prior art taught away from selecting an adjacent homolog as a lead compound. *Id.* at 1377-78. All of the references taught that an electron-withdrawing element was necessary, i.e., halogens such as fluorine, not ethyls. *Id.* at 1378. This Court's denial of the petition in *Eli Lilly* is certainly understandable. The closest prior art was well-outside the "objective reach of the claim" to olanzapine, and therefore nonobvious. *KSR*, 127 S. Ct. at 1742.

The contrast to this case could not be more stark. The closest prior art to pioglitazone was compound b, a compound that the prior art repeatedly quantified as the most potent antidiabetic. Not once, but at least four times in the prior-art period Takeda expressly promoted the potent antidiabetic activity of compound b: (1) in the '200 patent (SA30, col. 1, ll.4-6); (2) in an inventor declaration submitted as part of the '200 patent's prosecution history (SA43); (3) in Sohda II where compound b was shown to have double the potency than an unsubstituted pyridyl ring (SA48-53); and (4) when Takeda claimed compound b in the '779 patent as a pharmaceutical composition used to treat diabetes (SA19, claims 4, 6). A skilled artisan would not have missed these pronouncements in her review of the prior art.

II. Allowing the Federal Circuit's Application of the "Teaching, Suggestion, or Motivation" Test to Stand May Affect Thousands of Other Similarly Situated Cases

The TSM test as applied here forces a challenger to prove particular motivation in the prior art to select and modify the lead compound, which as asserted above, applies a rigid approach to structural obviousness and adds an onerous new motivation requirement for any challenger. Here, the Federal Circuit claimed that its requirement that Alphapharm show a motivation to select and modify a lead compound was "deciding the appeal as it has been argued." (A13.) But it is the province of the Federal Circuit to decide the case as the law requires. Here, the law required the Federal Circuit to decide the obviousness inquiry while following the strictures outlined in *KSR*. That is all the more important when the Federal Circuit's own law had been inconsistent with Supreme Court precedent and § 103 for many years, including those years this case was litigated and tried.

The Federal Circuit also created a dangerous precedent for all chemical obviousness cases concerning pharmaceuticals. Before this case, the standard for "teaching away" was strict. The prior art taken as a whole only taught away when the route to the invention was "unlikely to be productive of the result sought." *Medichem*, 437 F.3d at 1165. But the Federal Circuit appears to have abandoned that precedent, in at least chemical-compound cases, allowing teaching away even when the pioneer company obtains a patent on a compound using the route most promising—but not without side effects—from the prior art.

Pharmaceuticals are expected to have effects in the body other than their indicated use. It is the role of the medicinal chemist to reduce those effects to acceptable levels while maximizing efficacy. Now, under the evidently relaxed Federal Circuit patentability standard in this case, even the most minor side effect reported in the literature will be touted by a patentee as teaching the skilled person away from the invention. The result will be routine innovation in pharmaceuticals covered by patent monopolies at the expense of the public.

By addressing these missteps now, the Court will clarify and advance the progress of every issued U.S. patent claiming chemical compounds, every pending application claiming chemical compounds, and every litigation where a claim reciting a chemical compound is at issue. It is for these reasons that the Court should grant Alphapharm's petition.

CONCLUSION

Alphapharm respectfully requests that this Court grant the petition for a writ of certiorari, reverse the judgment of the Federal Circuit, and enter judgment that claims 1, 2, and 5 of the '777 patent are obvious as a matter of law.

Dated: December 20, 2007

Respectfully submitted,

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APPENDIX A — OPINION OF THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT DATED JUNE 28, 2007

UNITED STATES COURT OF APPEALS FEDERAL CIRCUIT

No. 06-1329.

TAKEDA CHEMICAL INDUSTRIES, LTD. and Takeda Pharmaceuticals North America, INC.,

Plaintiffs-Appellees,

v.

ALPHAPHARM PTY., LTD. and Genpharm, Inc.,

Defendants-Appellants.

June 28, 2007.

Before LOURIE, BRYSON, and DYK, Circuit Judges.

Opinion for the court filed by Circuit Judge LOURIE. Concurring opinion filed by Circuit Judge DYK.

LOURIE, Circuit Judge.

Alphapharm Pty., Ltd. and Genpharm, Inc. (collectively "Alphapharm") appeal from the decision of

the United States District Court for the Southern District of New York, following a bench trial, that U.S. Patent 4,687,777 was not shown to be invalid under 35 U.S.C. § 103. *Takeda Chem. Indus., Ltd. v. Mylan Labs.*, 417 F.Supp.2d 341 (S.D.N.Y.2006). Because we conclude that the district court did not err in determining that the claimed compounds would not have been obvious in light of the prior art, and hence that the patent has not been shown to be invalid, we affirm.

BACKGROUND

Diabetes is a disease that is characterized by the body's inability to regulate blood sugar. It is generally caused by inadequate levels of insulin-a hormone produced in the pancreas. Insulin allows blood sugar or glucose, which is derived from food, to enter into the body's cells and be converted into energy. There are two types of diabetes, known as Type 1 and Type 2. In Type 1 diabetes, the pancreas fails to produce insulin, and individuals suffering from this type of diabetes must regularly receive insulin from an external source. In contrast, Type 2 diabetic individuals produce insulin. However, their bodies are unable to effectively use the insulin that is produced. This is also referred to as insulin resistance. As a result, glucose is unable to enter the cells, thereby depriving the body of its main source of energy. Type 2 diabetes is the most common form of diabetes-affecting over 90% of diabetic individuals.

In the 1990s, a class of drugs known as thiazolidinediones ("TZDs") was introduced on the

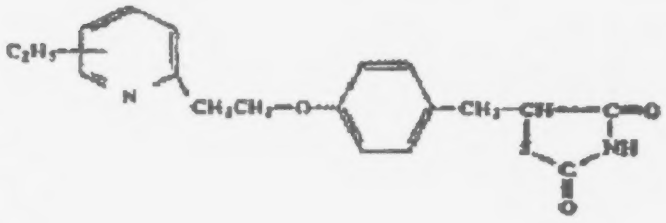
market as a treatment for Type 2 diabetes. Takeda Chemical Industries, Ltd., and Takeda Pharmaceuticals North America, Inc. (collectively "Takeda") first invented certain TZDs in the 1970s. Takeda's research revealed that TZDs acted as insulin sensitizers, *i.e.*, compounds that ameliorate insulin resistance. Although the function of TZDs was not completely understood, TZDs appeared to lower blood glucose levels by binding to a molecule in the nucleus of the cell known as PPARgamma, which activates insulin receptors and stimulates the production of glucose transporters. *Takeda*, 417 F.Supp.2d at 348-49. The transporters then travel to the cellular surface and enable glucose to enter the cell from the bloodstream. *Id.*

Takeda developed the drug ACTOS®, which is used to control blood sugar in patients who suffer from Type 2 diabetes. ACTOS® has enjoyed substantial commercial success since its launch in 1999. By 2003, it held 47% of the TZD market, and gross sales for that year exceeded $1.7 billion. *Id.* at 386. The active ingredient in ACTOS® is the TZD compound pioglitazone, a compound claimed in the patent in suit.

Takeda owns U.S. Patent 4,687,777 (the " '777 patent") entitled "Thiazolidinedione Derivatives, Useful As Antidiabetic Agents." The patent is directed to "compounds which can be practically used as antidiabetic agents having a broad safety margin between pharmacological effect and toxicity or unfavorable side reactions." '777 patent col.1 ll.34-37. The asserted claims are claims 1, 2, and 5. Claim 1 claims a genus of

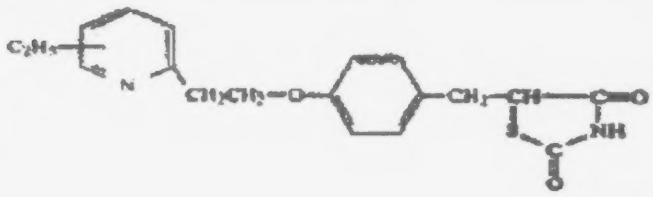
compounds. Claim 5 claims pharmaceutical compositions containing that genus of compounds. Those claims read as follows:

1. A compound of the formula:



or a pharmacologically acceptable salt thereof.

5. An antidiabetic composition which consists essentially of a compound of the formula:



or a pharmacologically acceptable salt thereof, in association with a pharmacologically acceptable carrier, excipient or diluent.

Id., claims 1 & 5.

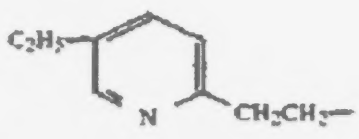
Appendix A

For purposes of this appeal, the critical portion of the compound structure is the left moiety of the molecule, namely, the ethyl-substituted pyridyl ring.[1] That chemical structure, which has an ethyl substituent (C^2 H^5) pictorially drawn to the center of the pyridyl ring, indicates that the structure covers four possible compounds, *viz.*, compounds with an ethyl substituent located at the four available positions on the pyridyl ring. *Takeda*, 417 F.Supp.2d at 360. The formula includes the 3-ethyl compound, 4-ethyl compound, 5-ethyl compound (pioglitazone), and 6-ethyl compound.

Claim 2 of the '777 patent covers the single compound pioglitazone. That claim, which depends from claim 1, reads:

> 2. A compound as claimed in claim 1, wherein the compound is 5-{4-[2-(5-ethyl-2-pyridyl)ethoxy] benzyl}-2,4-thiazolidinedione.

'777 patent, claim 2. Pioglitazone is referred to as the 5-ethyl compound because the ethyl substituent is attached to the 5-position on the pyridyl ring. That portion of the compound is depicted as:

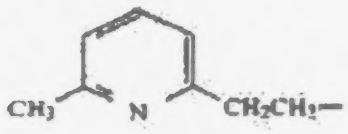


1. Pyridine is a "six-membered carbon-containing ring with one carbon replaced by a nitrogen." *Takeda*, 417 F.Supp.2d at 351.

Appendix A

Alphapharm, a generic drug manufacturer, filed an Abbreviated New Drug Application ("ANDA") pursuant to the Hatch-Waxman Act seeking U.S. Food and Drug Administration ("FDA") approval under 21 U.S.C. § 355(j) et seq. to manufacture and sell a generic version of pioglitazone. Alphapharm filed a Paragraph IV certification with its ANDA pursuant to § 505(j)(2)(B)(ii), asserting that the '777 patent is invalid as obvious under 35 U.S.C. § 103. In response, Takeda sued Alphapharm, along with three other generic drug manufacturers who also sought FDA approval to market generic pioglitazone, alleging that the defendants have infringed or will infringe the '777 patent.

On January 17, 2006, the district court commenced a bench trial solely on the issues of validity and enforceability of the '777 patent. Alphapharm advanced its invalidity argument, asserting that the claimed compounds would have been obvious at the time of the alleged invention. Alphapharm's obviousness contention rested entirely on a prior art TZD compound that is referenced in Table 1 of the '777 patent as compound b. The left moiety of compound b consists of a pyridyl ring with a methyl (CH^3) group attached to the 6-position of the ring. That portion of its chemical structure is illustrated as follows:



Alphapharm asserted that the claimed compounds would have been obvious over compound b.

The district court found that Alphapharm failed to prove by clear and convincing evidence that the asserted claims were invalid as obvious under 35 U.S.C. § 103. The court first concluded that there was no motivation in the prior art to select compound b as the lead compound for antidiabetic research, and that the prior art taught away from its use. As such, the court concluded that Alphapharm failed to make a prima facie case of obviousness. The court continued its analysis and found that even if Alphapharm succeeded in making a prima facie showing, Takeda would still prevail because any prima facie case of obviousness was rebutted by the unexpected results of pioglitazone's nontoxicity. The court then rendered judgment in favor of Takeda. The district court also held that the '777 patent had not been procured though inequitable conduct. That decision has been separately appealed and has been affirmed in a decision issued today.

Alphapharm timely appealed. We have jurisdiction pursuant to 28 U.S.C. § 1295(a)(1).

DISCUSSION

A. Standard of Review

In this appeal, we are presented with one issue, namely, whether the asserted claims of the '777 patent would have been obvious under 35 U.S.C. § 103 at the

time the invention was made. An invention is not patentable, *inter alia*, "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Because a patent is presumed to be valid, 35 U.S.C. § 282, the evidentiary burden to show facts supporting a conclusion of invalidity, which rests on the accused infringer, is one of clear and convincing evidence. *AK Steel Corp. v. Sollac & Ugine*, 344 F.3d 1234, 1238-39 (Fed.Cir.2003). Whether an invention would have been obvious under 35 U.S.C. § 103 is a "question of law, reviewed de novo, based upon underlying factual questions which are reviewed for clear error following a bench trial." *Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286, 1289 (Fed.Cir.2006).

B. Obviousness

Alphapharm raises three main arguments in support of its contention that the claims would have been obvious. First, Alphapharm asserts that the district court misapplied the law, particularly the law governing obviousness in the context of structurally similar chemical compounds. According to Alphapharm, the record established that compound b was the most effective antidiabetic compound in the prior art, and thus the court erred by failing to apply a presumption that one of ordinary skill in the art would have been motivated to make the claimed compounds. Alphapharm asserts that such a conclusion is mandated by our case law,

including our en banc decision in *In re Dillon*, 919 F.2d 688 (Fed.Cir.1990). Second, Alphapharm argues that the court erred in determining the scope and content of the prior art, in particular, whether to include the prosecution history of the prior '779 patent. Lastly, Alphapharm assigns error to numerous legal and factual determinations and certain evidentiary rulings that the court made during the course of the trial.

Takeda responds that the district court correctly determined that Alphapharm failed to prove by clear and convincing evidence that the asserted claims are invalid as obvious. Takeda contends that there was overwhelming evidence presented at trial to support the court's conclusion that no motivation existed in the prior art for one of ordinary skill in the art to select compound b as a lead compound, and even if there was, that the unexpected results of pioglitazone's improved toxicity would have rebutted any prima facie showing of obviousness. Takeda further argues that all of Alphapharm's remaining challenges to the district court's legal and factual rulings are simply without merit.

We agree with Takeda that the district court did not err in concluding that the asserted claims of the '777 patent would not have been obvious. The Supreme Court recently addressed the issue of obviousness in *KSR International Co. v. Teleflex Inc.*, __ U.S. __, 127 S.Ct. 1727, 167 L.Ed.2d 705 (2007). The Court stated that the *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966), factors still control an obviousness inquiry. Those factors are: 1) "the scope

and content of the prior art"; 2) the "differences between the prior art and the claims"; 3) "the level of ordinary skill in the pertinent art"; and 4) objective evidence of nonobviousness. *KSR*, 127 S.Ct. at 1734 (quoting *Graham*, 383 U.S. at 17-18, 86 S.Ct. 684).

In a thorough and well-reasoned opinion, albeit rendered before *KSR* was decided by the Supreme Court, the district court made extensive findings of fact and conclusions of law as to the four *Graham* factors. Alphapharm's arguments challenge the court's determinations with respect to certain of these factors, which we now address.

1. Differences Between the Prior Art and the Claims

a. Selection of Compound b as Lead Compound

Alphapharm's first argument challenges the court's determination with regard to the "differences between the prior art and the claims." Alphapharm contends that the court erred as a matter of law in holding that the ethyl-substituted TZDs were nonobvious in light of the closest prior art compound, compound b, by misapplying the law relating to obviousness of chemical compounds.

We disagree. Our case law concerning prima facie obviousness of structurally similar compounds is well-established. We have held that "structural similarity between claimed and prior art subject matter, proved

by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." *Dillon,* 919 F.2d at 692. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of "adequate support in the prior art" for the change in structure. *In re Grabiak,* 769 F.2d 729, 731-32 (Fed.Cir.1985).

We elaborated on this requirement in the case of *In re Deuel,* 51 F.3d 1552, 1558 (Fed.Cir.1995), where we stated that "[n]ormally a prima facie case of obviousness is based upon structural similarity, *i.e.,* an established structural relationship between a prior art compound and the claimed compound." That is so because close or established "[s]tructural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds." *Id.* A known compound may suggest its homolog, analog, or isomer because such compounds "often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." *Id.* We clarified, however, that in order to find a prima facie case of unpatentability in such instances, a showing that the "prior art would have suggested making the specific molecular modifications necessary to achieve the claimed invention" was also required. *Id.* (citing *In re Jones,* 958 F.2d 347 (Fed.Cir.1992); *Dillon,* 919 F.2d 688; *Grabiak,* 769 F.2d 729; *In re Lalu,* 747 F.2d 703 (Fed.Cir.1984)).

That test for prima facie obviousness for chemical compounds is consistent with the legal principles enunciated in *KSR*.[2] While the *KSR* Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in an obviousness inquiry, the Court acknowledged the importance of identifying "a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does" in an obviousness determination. *KSR*, 127 S.Ct. at 1731. Moreover, the Court indicated that there is "no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis." *Id.* As long as the test is not applied as a "rigid and mandatory" formula, that test can provide "helpful insight" to an obviousness inquiry. *Id.* Thus, in cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.

We agree with Takeda and the district court that Alphapharm failed to make that showing here.

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2. We note that the Supreme Court in its *KSR* opinion referred to the issue as whether claimed subject matter "was" or "was not" obvious. Since 35 U.S.C. § 103 uses the language "would have been obvious," and the Supreme Court in *KSR* did consider the particular time at which obviousness is determined, we consider that the Court did not in *KSR* reject the standard statutory formulation of the inquiry whether the claimed subject matter "would have been obvious at the time the invention was made." 35 U.S.C. § 103. Hence, we will continue to use the statutory "would have been" language.

Alphapharm argues that the prior art would have led one of ordinary skill in the art to select compound b as a lead compound. By "lead compound," we understand Alphapharm to refer to a compound in the prior art that would be most promising to modify in order to improve upon its antidiabetic activity and obtain a compound with better activity.[3] Upon selecting that compound for antidiabetic research, Alphapharm asserts that one of ordinary skill in the art would have made two obvious chemical changes: first, homologation, *i.e.*, replacing the methyl group with an ethyl group, which would have resulted in a 6-ethyl compound; and second, "ring-walking," or moving the ethyl substituent to another position on the ring, the 5-position, thereby leading to the discovery of pioglitazone. Thus, Alphapharm's obviousness argument clearly depends on a preliminary finding that one of ordinary skill in the art would have selected compound b as a lead compound.

The district court found, however, that one of ordinary skill in the art would not have selected compound b as the lead compound. In reaching its determination, the court first considered Takeda's U.S. Patent 4,287,200 (the " '200 patent"), which was issued on September 1, 1981, and its prosecution history. The court found that the '200 patent "discloses hundreds of

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3. The parties do not dispute that compound b was the closest prior art compound. Thus, the legal question is whether or not the claimed subject matter would have been obvious over that compound. We will, however, use Alphapharm's terminology of "lead compound" in this opinion, deciding the appeal as it has been argued.

millions of TZD compounds."[4] *Takeda*, 417 F.Supp.2d at 378. The patent specifically identified fifty-four compounds, including compound b, that were synthesized according to the procedures described in the patent, but did not disclose experimental data or test results for any of those compounds. The prosecution history, however, disclosed test results for nine specific compounds, including compound b. That information was provided to the examiner in response to a rejection in order to show that the claimed compounds of the '200 patent were superior to the known compounds that were disclosed in a cited reference. The court, however, found nothing in the '200 patent, or in its file history, to suggest to one of ordinary skill in the art that those nine compounds, out of the hundreds of millions of compounds covered by the patent application, were the best performing compounds as antidiabetics, and hence targets for modification to seek improved properties. *Id.* at 375.

The court next considered an article that was published the following year in 1982 by T. Sodha et al. entitled "Studies on Antidiabetic Agents. II. Synthesis of 5-[4-(1-Methylcyclohexylmethoxy)-benzyl]thia zolidine-2,4-dione (ADD-3878) and Its Derivatives" ("Sodha II"). The Sodha II reference disclosed data relating to hypoglycemic activity and plasma triglyceride

4. Three divisional applications derive from the '200 patent. Those applications matured into U.S. Patent 4,340,605, U.S. Patent 4,438,141, and U.S. Patent No. 4,444,779 (the " '779 Patent"). The '779 patent is of particular relevance in this appeal and is discussed below. *Takeda*, 417 F.Supp.2d at 378.

lowering activity for 101 TZD compounds. Those compounds did not include pioglitazone, but included compound b. Significantly, Sodha II identified three specific compounds that were deemed most favorable in terms of toxicity and activity. Notably, compound b was not identified as one of the three most favorable compounds. On the contrary, compound b, was singled out as causing "considerable increases in body weight and brown fat weight."

The court also considered Takeda's '779 patent. That patent covers a subset of compounds originally included in the '200 patent application, namely, TZD compounds "where the pyridyl or thiazolyl groups may be substituted." *Id.* at 353. The broadest claim of the '779 patent covers over one million compounds. *Id.* at 378. Compound b was specifically claimed in claim 4 of the patent. The court noted that a preliminary amendment in the prosecution history of the patent contained a statement that "the compounds in which these heterocyclic rings are substituted have become important, especially [compound b]." *Id.*

Based on the prior art as a whole, however, the court found that a person of ordinary skill in the art would not have selected compound b as a lead compound for antidiabetic treatment. Although the prosecution history of the '779 patent included the statement that characterized compound b as "especially important," the court found that any suggestion to select compound b was essentially negated by the disclosure of the Sodha II reference. The court reasoned that one of ordinary

skill in the art would not have chosen compound b, notwithstanding the statement in the '779 patent prosecution history, "given the more exhaustive and reliable scientific analysis presented by Sodha II, which taught away from compound b, and the evidence from all of the TZD patents that Takeda filed contemporaneously with the '779 [p]atent showing that there were many promising, broad avenues for further research." *Id.* at 380.

The court found that the three compounds that the Sodha II reference identified as "most favorable" and "valuable for the treatment of maturity-onset diabetes," not compound b, would have served as the best "starting point for further investigation" to a person of ordinary skill in the art. *Id.* at 376. Because diabetes is a chronic disease and thus would require long term treatment, the court reasoned that researchers would have been dissuaded from selecting a lead compound that exhibited negative effects, such as toxicity, or other adverse side effects, especially one that causes "considerable increases in body weight and brown fat weight." *Id.* at 376-77. Thus, the court determined that the prior art did not suggest to one of ordinary skill in the art that compound b would be the best candidate as the lead compound for antidiabetic research.

Admissions from Alphapharm witnesses further buttressed the court's conclusion. Dr. Rosenberg, head of Alphapharm's intellectual property department, testified as a 30(b)(6) witness on behalf of Alphapharm. In discussing Sodha II, Dr. Rosenberg admitted that

there was nothing in the article that would recommend that a person of ordinary skill in the art choose compound b over other compounds in the article that had the same efficacy rating. Dr. Rosenberg, acknowledging that compound b had the negative side effects of increased body weight and brown fat, also admitted that a compound with such side effects would "presumably not" be a suitable candidate compound for treatment of Type II diabetes. Alphapharm's expert, Dr. Mosberg, concurred in that view at his deposition when he admitted that a medicinal chemist would find such side effects "undesirable."

Moreover, another Alphapharm 30(b)(6) witness, Barry Spencer, testified at his deposition that in reviewing the prior art, one of ordinary skill in the art would have chosen three compounds in Sodha II as lead compounds for research, not solely compound b. In addition, Takeda's witness, Dr. Morton, testified that at the time Sodha II was published, it was known that obesity contributed to insulin resistance and Type 2 diabetes. Thus, one of ordinary skill in the art would have concluded that Sodha II taught away from pyridyl compounds because it associated adverse side effects with compound b.

We do not accept Alphapharm's assertion that *KSR*, as well as another case recently decided by this court, *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348 (Fed.Cir.2007), mandates reversal. Relying on *KSR*, Alphapharm argues that the claimed compounds would have been obvious because the prior art compound fell within "the objective

reach of the claim," and the evidence demonstrated that using the techniques of homologation and ring-walking would have been "obvious to try." Additionally, Alphapharm argues that our holding in *Pfizer*, where we found obvious certain claims covering a particular acid-addition salt, directly supports its position.

We disagree. The *KSR* Court recognized that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 127 S.Ct. at 1732. In such circumstances, "the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.* That is not the case here. Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative properties that would have directed one of ordinary skill in the art away from that compound. Thus, this case fails to present the type of situation contemplated by the Court when it stated that an invention may be deemed obvious if it was "obvious to try." The evidence showed that it was not obvious to try.

Similarly, Alphapharm's reliance on *Pfizer* fares no better. In *Pfizer*, we held that certain claims covering the besylate salt of amlodipine would have been obvious. The prior art included a reference, referred to as

the Berge reference, that disclosed a genus of pharmaceutically acceptable anions that could be used to form pharmaceutically acceptable acid addition salts, as well as other publications that disclosed the chemical characteristics of the besylate salt. *Pfizer*, 480 F.3d at 1363. Noting that our conclusion was based on the "particularized facts of this case," we found that the prior art provided "ample motivation to narrow the genus of 53 pharmaceutically-acceptable anions disclosed by Berge to a few, including benzene sulphonate." *Id.* at 1363, 1367. Here, the court found nothing in the prior art to narrow the possibilities of a lead compound to compound b. In contrast, the court found that one of ordinary skill in the art would have chosen one of the many compounds disclosed in Sodha II, of which there were over ninety, that "did not disclose the existence of toxicity or side effects, and to engage in research to increase the efficacy and confirm the absence of toxicity of those compounds, rather than to choose as a starting point a compound with identified adverse effects." Thus, *Pfizer* does not control this case.

Based on the record before us, we conclude that the district court's fact-findings were not clearly erroneous and were supported by evidence in the record. Moreover, we reject the assertion that the court failed to correctly apply the law relating to prima facie obviousness of chemical compounds. Because Alphapharm's obviousness argument rested entirely on the court making a preliminary finding that the prior art would have led to the selection of compound b as the lead compound, and Alphapharm failed to prove that

assertion, the court did not commit reversible error by failing to apply a presumption of motivation. We thus conclude that the court did not err in holding that Alphapharm failed to establish a prima facie case of obviousness. *See Eli Lilly & Co. v. Zenith Goldline Pharms.*, 471 F.3d 1369 (Fed.Cir.2006) (affirming the district court's finding of nonobviousness upon concluding, in part, that the prior art compound would not have been chosen as a lead compound).

b. Choice of the Claimed Compounds

Even if Alphapharm had established that preliminary finding, and we have concluded that it did not, the record demonstrates that Alphapharm's obviousness argument fails on a second ground. The district court found nothing in the prior art to suggest making the specific molecular modifications to compound b that are necessary to achieve the claimed compounds. In reaching that conclusion, the court first found that the process of modifying lead compounds was not routine at the time of the invention. *Takeda*, 417 F.Supp.2d at 380. Dr. Mosberg opined that the steps of homologation and ring-walking were "routine steps in the drug optimization process," but the court found that testimony unavailing in light of the contrary, more credible, testimony offered by Takeda's experts. *Id.* at 381. In addition, the court relied on Dr. Rosenberg's admission that a person of ordinary skill in the art would "look at a host of substituents, such as chlorides, halides and others, not just methyls" in modifying the pyridyl ring. *Id.*

Appendix A

Pioglitazone differs from compound b in two respects, and one would have to both homologate the methyl group of compound b and move the resulting ethyl group to the 5-position on the pyridyl ring in order to obtain pioglitazone. With regard to homologation, the court found nothing in the prior art to provide a reasonable expectation that adding a methyl group to compound b would reduce or eliminate its toxicity. Based on the test results of the numerous compounds disclosed in Sodha II, the court concluded that "homologation had no tendency to decrease unwanted side effects" and thus researchers would have been inclined "to focus research efforts elsewhere." *Id.* at 383. Indeed, several other compounds exhibited similar or better potency than compound b, and one compound in particular, compound 99, that had no identified problems differed significantly from compound b in structure. *Id.* at 376 n. 51. Moreover, Dr. Mosberg agreed with Takeda's expert, Dr. Danishefsky, that the biological activities of various substituents were "unpredictable" based on the disclosure of Sodha II. *Id.* at 384-85. The court also found nothing in the '200 and '779 patents to suggest to one of ordinary skill in the art that homologation would bring about a reasonable expectation of success.

As for ring-walking, the court found that there was no reasonable expectation in the art that changing the positions of a substituent on a pyridyl ring would result in beneficial changes. Dr. Mosberg opined that the process of ring-walking was "known" to Takeda, but the court found that testimony inapt as it failed to support a reasonable expectation to one of ordinary skill in the art

that performing that chemical change would cause a compound to be more efficacious or less toxic. *Id.* at 382. Moreover, Dr. Mosberg relied on the efficacy data of phenyl compounds in Sodha II, but the court found those data insufficient to show that the same effects would occur in pyridyl compounds.

Alphapharm relies on *In re Wilder,* 563 F.2d 457 (CCPA 1977), for the proposition that differences in a chemical compound's properties, resulting from a small change made to the molecule, are reasonably expected to vary by degree and thus are insufficient to rebut a prima facie case of obviousness. In *Wilder,* our predecessor court affirmed the Board's holding that a claimed compound, which was discovered to be useful as a rubber antidegradant and was also shown to be nontoxic to human skin, would have been obvious in light of its homolog and isomer that were disclosed in the prior art. The evidence showed that the homolog was similarly nontoxic to the human skin, whereas the isomer was toxic. The court held that "one who claims a compound, per se, which is structurally similar to a prior art compound must rebut the presumed expectation that the structurally similar compounds have similar properties." *Id.* at 460. While recognizing that the difference between the isomer's toxicity and the nontoxicity of the homolog and claimed compound "indicate[d] some degree of unpredictability," the court found that the appellant failed to "point out a single actual difference in properties between the claimed compound and the homologue," and thus failed to rebut the presumption. *Wilder,* 563 F.2d at 460.

Appendix A

We would note that since our *Wilder* decision, we have cautioned "that generalization should be avoided insofar as specific chemical structures are alleged to be prima facie obvious one from the other," *Grabiak*, 769 F.2d at 731. In addition to this caution, the facts of the present case differ significantly from the facts of Wilder. Here, the court found that pioglitazone exhibited unexpectedly superior properties over the prior art compound b. *Takeda*, 417 F.Supp.2d at 385. The court considered a report entitled "Preliminary Studies on Toxicological Effects of Ciglitazone-Related Compounds in the Rats" that was presented in February 1984 by Dr. Takeshi Fujita, then-Chief Scientist of Takeda's Biology Research Lab and co-inventor of the '777 patent. That report contained results of preliminary toxicity studies that involved selected compounds, including pioglitazone and compound b. Compound b was shown to be "toxic to the liver, heart and erythrocytes, among other things," whereas pioglitazone was "comparatively potent" and "showed no statistically significant toxicity." *Id.* at 356-57. During the following months, Takeda performed additional toxicity studies on fifty compounds that had been already synthesized and researched by Takeda, including pioglitazone. The compounds were tested for potency and toxicity. The results were presented in another report by Fujita entitled "Pharmacological and Toxicological Studies of Ciglitazone and Its Analogues." Pioglitazone was shown to be the only compound that exhibited no toxicity, although many of the other compounds were found to be more potent. *Id.* at 358.

Thus, the court found that there was no reasonable expectation that pioglitazone would possess the desirable property of nontoxicity, particularly in light of the toxicity of compound b. The court's characterization of pioglitazone's unexpected results is not clearly erroneous. As such, *Wilder* does not aid Alphapharm because, unlike the homolog and claimed compound in *Wilder* that shared similar properties, pioglitazone was shown to differ significantly from compound b, of which it was not a homolog, in terms of toxicity. Consequently, Takeda rebutted any presumed expectation that compound b and pioglitazone would share similar properties.

Alphapharm also points to a statement Takeda made during the prosecution of the '779 patent as evidence that there was a reasonable expectation that making changes to the pyridyl region of compound b would lead to "better toxicity than the prior art." During prosecution of the '779 patent, in response to an enablement rejection, Takeda stated that "there should be no reason in the instant case for the Examiner to doubt that the claimed compounds having the specified substituent would function as a hypolipidemic and hypoglycemic agent as specified in the instant disclosure." That statement, however, indicates only that changes to the left moiety of a lead compound would create compounds with the same properties as the compounds of the prior art; it does not represent that lower toxicity would result. And even if the statement did so represent, it does not refer to any specific substituent at any specific position of TZD's left moiety as particularly promising. As the court

correctly noted, the compounds disclosed in the '779 patent included a variety of substituents, including lower alkyls, halogens, and hydroxyl groups, attached to a pyridyl or thiazolyl group. As discussed *supra*, the district court found that the claims encompassed over one million compounds. Thus, we disagree with Alphapharm that that statement provided a reasonable expectation to one of ordinary skill in the art that performing the specific steps of replacing the methyl group of the 6-methyl compound with an ethyl group, and moving that substituent to the 5-position of the ring, would have provided a broad safety margin, particularly in light of the district court's substantiated findings to the contrary.

We thus conclude that Alphapharm's challenges fail to identify grounds for reversible error. The court properly considered the teachings of the prior art and made credibility determinations regarding the witnesses at trial. We do not see any error in the district court's determination that one of ordinary skill in the art would not have been prompted to modify compound b, using the steps of homologation and ring-walking, to synthesize the claimed compounds. Because the court's conclusions are not clearly erroneous and are supported by the record evidence, we find no basis to disturb them.

The court properly concluded that Alphapharm did not make out a prima facie case of obviousness because Alphapharm failed to adduce evidence that compound b would have been selected as the lead compound and, even if that preliminary showing had been made, it failed to

show that there existed a reason, based on what was known at the time of the invention, to perform the chemical modifications necessary to achieve the claimed compounds.

In light of our conclusion that Alphapharm failed to prove that the claimed compounds would have been prima facie obvious, we need not consider any objective indicia of nonobviousness.[5]

2. Scope and Content of the Prior Art

Alphapharm also assigns error to the district court's determination regarding the scope and content of the prior art. Alphapharm asserts that the court excluded the prosecution history of the '779 patent from the scope of the prior art after wrongly concluding that it was not accessible to the public. Takeda responds that the court clearly considered the '779 patent prosecution history, which was admitted into evidence on the first day of testimony. Takeda urges that the court's consideration of the prosecution history is apparent based on its extensive analysis of the '779 patent and the file history that appears in the court's opinion.

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5. The concurrence, while agreeing that the question of the "overbreadth" of claims 1 and 5 has been waived, states further that the 6-ethyl compound, which is within the scope of claims 1 and 5, has not been shown to possess unexpected results sufficient to overcome a prima facie case of obviousness, and hence claims 1 and 5 are likely invalid as obvious. Since waiver is sufficient to answer the point being raised, no further comment need be made concerning its substance.

We agree with Takeda that the district court did not err in its consideration of the scope of the prior art. As discussed above, the court considered the prosecution history, and even expressly considered one of the key statements in the prosecution history upon which Alphapharm relies in support of its position that compound b would have been chosen as the lead compound. *Takeda*, 417 F.Supp.2d at 378. In considering the prosecution history of the '779 patent, the court noted that Takeda filed a preliminary amendment on March 15, 1983, in which its prosecuting attorney stated that "the compounds in which these heterocyclic rings are substituted have become important, especially [the 6-methyl compound]." *Id.* The court rejected Alphapharm's assertion that that statement supported the conclusion that compound b would have been selected as a lead compound. Rather, the court found that viewing the prior art as a whole, the prior art showed "that Takeda was actively conducting research in many directions, and had not narrowed its focus to compound b." *Id.* at 379. Thus, while the district court may have incorrectly implied that prosecution histories are not accessible to the public, *see id.* at n. 59, *see also Custom Accessories, Inc. v. Jeffrey-Allan Indus.*, 807 F.2d 955 (Fed.Cir.1986) ("[t]he person of ordinary skill is a hypothetical person who is presumed to be aware of all the pertinent prior art"), the court nonetheless considered the prosecution history of the '779 patent in its obviousness analysis and accorded proper weight to the statements contained therein. Thus, any error committed by the court in this regard was harmless error.

We have considered Alphapharm's remaining arguments and find none that warrant reversal of the district court's decision.

CONCLUSION

We affirm the district court's determination that claims 1, 2, and 5 of the '777 patent have not been shown to have been obvious and hence invalid.

AFFIRMED

Concurring opinion filed by Circuit Judge DYK.

DYK, Circuit Judge, concurring.

I join the opinion of the court insofar as it upholds the district court judgment based on a determination that a claim to pioglitazone (the 5-ethyl compound) would be non-obvious over the prior art. The problem is that only one of the three claims involved here-claim 2-is limited to pioglitazone. In my view, the breadth of the other two claims, claims 1 and 5 of U.S. Patent No. 4,867,777 (" '777 patent")—which are also referenced in the judgment-renders them likely invalid.

All of the compounds claimed in claims 1, 2 and 5 were included in generic claims in the prior art U.S. Patent No. 4,287,200 (" '200 patent"). Unfortunately our law concerning when a species is patentable over a genus claimed in the prior art is less than clear. It is, of course, well established that a claim to a genus does not

necessarily render invalid a later claim to a species within that genus. *See Eli Lilly & Co. v. Bd. of Regents of Univ. of Wash.*, 334 F.3d 1264, 1270 (Fed.Cir.2003). In my view a species should be patentable over a genus claimed in the prior art only if unexpected results have been established. Our case law recognizes the vital importance of a finding of unexpected results, both in this context and in the closely related context where a prior art patent discloses a numerical range and the patentee seeks to claim a subset of that range. *See Application of Petering*, 49 C.C.P.A. 993, 301 F.2d 676, 683 (1962) (species found patentable when genus claimed in prior art because unexpected properties of the species were shown); *see also Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed.Cir.2007) (relying on lack of unexpected results in determining that species claim was obvious in view of prior art genus claim); *In re Woodruff*, 919 F.2d 1575, 1578 (Fed.Cir.1990) (when applicant claims a subset of a range disclosed in a prior art patent, the applicant must generally show that "the claimed range achieves unexpected results relative to the prior art range.").

While the 5-ethyl compound (pioglitazone) is within the scope of the '200 patent, there is clear evidence, as the majority correctly finds, of unexpected results regarding that compound, and therefore its validity is not in question on this ground. However, at oral argument the patentee admitted that the prior art '200 patent also generically covers the 6-ethyl compound, which is within the scope of claims 1 and 5 of the '777 patent, and admitted that there is no evidence of

unexpected results for the 6-ethyl compound. Under such circumstances, I believe that the 6-ethyl is likely obvious, and consequently claims 1 and 5 are likely invalid for obviousness. However, the argument as to the overbreadth of claims 1 and 5 has been waived, because it was not raised in the opening brief. In any event, as a practical matter, the judgment finding that the appellants' filing of the ANDA for pioglitazone is an infringement and barring the making of pioglitazone is supported by the finding that claim 2 standing alone is not invalid and is infringed.

APPENDIX B — OPINION AND ORDER OF THE UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF NEW YORK DATED FEBRUARY 21, 2006

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

Nos. 03 Civ.8253(DLC)
04 Civ.1966(DLC).

TAKEDA CHEMICAL INDUSTRIES, LTD. and Takeda Pharmaceuticals North America, Inc.,

Plaintiffs,

v.

MYLAN LABORATORIES, INC., Mylan Pharmaceuticals, Inc., and UDL Laboratories, Inc.,

Defendants.

Takeda Chemical Industries, Ltd. and Takeda Pharmaceuticals North America, Inc.,

Plaintiffs,

v.

Alphapharm Pty. Ltd. and Genpharm, Inc.,

Defendants.

Appendix B

Feb. 21, 2006.

OPINION & ORDER

COTE, District Judge.

Takeda Pharmaceutical Company Limited ("Takeda") and Takeda Pharmaceuticals North America, Inc. ("Takeda North America") have brought this patent action under the Food Drug Cosmetic Act, 21 U.S.C. §§ 301-99, the Drug Price Competition and Patent Term Restoration Act of 1984, Pub L. No. 98-417, 98 Stat. 1585 (1984) (codified in scattered sections of titles 21, 35, and 42 U.S.C.) (the "Hatch-Waxman Act"), and under the patent laws of the United States, alleging that four generic drug manufacturers have infringed and will induce infringement of Takeda's patents protecting its product ACTOS®, a drug used to treat Type 2 diabetes.

This Opinion presents the findings of fact and conclusions of law following a bench trial held between January 17 and January 30, 2006, to resolve the challenges made by defendants to Takeda's U.S. Patent No. 4,687,777 (" '777 Patent"), which protects the invention of the chemical compound 5-% 8B4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl}-2,4-thiazolidinedione ("pioglitazone"). Alphapharm Pty. Ltd. and Genpharm, Inc. ("Alphapharm") contend that the invention is obvious based on the disclosure by Takeda of a structurally similar molecule in the prior art. Mylan Laboratories, Inc., Mylan Pharmaceuticals, Inc., and UDL Laboratories, Inc. ("Mylan") contend that Takeda

deceived the Patent and Trademark Office ("PTO") when it applied for the '777 Patent, principally by misrepresenting the results of efficacy and toxicity tests. Neither challenge is meritorious. The length of this Opinion is occasioned by the need to address the many iterations of the defendants' arguments, as they searched for a viable theory to attack the '777 Patent.

As described below, the '777 Patent discloses a remarkable invention. After decades of work to develop an anti-diabetic treatment, Takeda discovered a pharmaceutical agent that was both effective and non-toxic. This represented a significant advance over compounds disclosed in the prior art. Takeda's application to the PTO for the '777 Patent reported the very analysis of test results on which Takeda itself had previously relied to select the pioglitazone molecule from the thousands it had synthesized and the hundreds it had tested. Faced with the task of proving their cases by clear and convincing evidence, both Alphapharm and Mylan have failed to make even a rudimentary showing that the invention was obvious or that Takeda engaged in inequitable conduct. Their challenges to the '777 Patent are rejected.

Trial Procedure

The trial was conducted in accordance with the Court's Individual Practices and the Scheduling Order dated July 20, 2004. The parties filed a Joint Pretrial Order and accompanying memoranda of law and proposed findings of fact and conclusions of law on

November 18, 2005. The parties also served affidavits containing the direct testimony of all their witnesses, as well as copies of all the exhibits and deposition testimony which they intended to offer as evidence in chief at trial.

A science tutorial was held on December 1, 2005. Testifying for Takeda were Silvio Inzucchi ("Inzucchi"), a Professor of Medicine at Yale University and expert endocrinologist who serves as the Director of the Yale Diabetes Center; James Hendrickson ("Hendrickson"), the Henry F. Fischbach Professor of Chemistry, retired, at Brandeis University and an expert in organic chemistry; and Peter Valberg, a senior scientist at a private environmental health consulting firm, an expert in the statistical analysis of animal testing data, and formerly an Associate Professor of Physiology at Harvard's School of Public Health. Testifying for Alphapharm was Henry Mosberg ("Mosberg"), a Professor of Medicinal Chemistry at the University of Michigan, and an expert in drug design. Testifying for Mylan was Lawrence Hendry ("Hendry"), an Adjunct Professor of Physiology and Endocrinology at the Medical College of Georgia, an Associate Adjunct Professor of Medicinal Chemistry at the University of Georgia, and the founder of a chemical design firm.

The plaintiffs and defendants were each given twenty-four hours for opening statements, examination of witnesses and evidentiary arguments at trial. Of the time granted the defendants, Alphapharm was given

eight hours and Mylan sixteen hours.[1] The parties were given additional time for summations.

In addition to the experts who testified on December 1, the following witnesses testified at trial. For Takeda, Richard Daly, Senior Vice President of Marketing at Takeda North America; William Kettyle ("Kettyle"), an expert endocrinologist with significant expertise in the treatment of diabetes; Loren Koller ("Koller"), a doctor in veterinary medicine, an environmental health and toxicology consultant, an expert in immunotoxicology, and an officer of the Association for Assessment and Accreditation of Laboratory Animal Care International; Takeshi Fujita ("Fujita"), a former Takeda employee who, as the Chief Scientist of Takeda's Biology Research Laboratory, was the co-inventor on the '777 Patent; Samuel Danishefsky ("Danishefsky"), a Professor of Chemistry at Columbia University who holds the Kettering Chair at the Memorial Sloan-Kettering Cancer Institute; Yasuo Sugiyama, Takeda's Manager of Strategic Research Planning and a researcher who was involved in the development of pioglitazone; Bernard Landau ("Landau"), a Professor of Biochemistry at Case and Western Reserve University, and, in 1996, a Nobel Fellow at the Karolinska Institute in Sweden; Bruce Stoner ("Stoner"), a former Chief Administrative Patent Judge; Gerard Colca ("Colca"), a former senior research scientist in metabolic disease research at The Upjohn Company ("Upjohn"), a U.S. pharmaceutical company

1. When the defendants exhausted their time at trial, they were given a limited amount of additional time.

that had worked with Takeda in the development of pioglitazone; and Douglas Morton, a former Director of Diabetes and Gastrointestinal Diseases Research at Upjohn.

Testifying for Alphapharm was Richard Wright, a Professor of Economics at the University of California at Berkeley, and a member of the Steering Committee for Berkeley's Center for Hunger and Obesity. Testifying for Mylan was Martin Ronis ("Ronis"), a Professor of Medicinal Sciences at the University of Arkansas, Associate Director of the Arkansas Childrens' Nutrition Center and an expert in chemical testing in animals. Mylan also presented the declaration of Mark Nusbaum ("Nusbaum"), a former Examiner-in-Chief and member of the Board of Patent Appeal and Interferences.[2]

The parties also offered excerpts from the deposition testimony of some of the fact witnesses that testified at trial and of the following individuals: Michael Davis, the American patent attorney who prosecuted the '777 Patent; Yoshikazu Hasagawa, the Senior Manager in charge of Intellectual Property litigation for Takeda; Shelly Monteleone, Intellectual Property Counsel for Mylan; Brett Mooney, an Alphapharm employee involved in pharmaceutical development; Hiroyuki Odaka, a former Takeda employee who worked in Takeda's Biology Research Laboratories at the time of the development of pioglitazone; Brian Roman, an attorney

2. Takeda chose not to cross-examine Nusbaum and thus he did not appear at trial.

and a Rule 30(b)(6) witness for Mylan; Howard Rosenberg ("Rosenberg"), the Group Intellectual Property and API Strategy Director for Generics U.K., a sister company of Alphapharm, and an Alphapharm Rule 30(b)(6) witness; Michael Rosenberg, the owner of Health Decisions, a company engaged in clinical research; Takashi Sohda, General Manager of Takeda's Pharmaceutical Research Division; Barry Spencer, a Senior Patent Officer at Alphapharm and a Rule 30(b)(6) witness for Alphapharm; Shigehisa Taketomi, a Takeda employee and Rule 30(b)(6) witness for Takeda; and Stephen Talton, a Mylan employee responsible for preparing applications to sell generic drugs.

The findings of fact based on the evidence presented at trial are scattered throughout this Opinion. The background section contains the story of the development of pioglitazone, an introduction to the prior art, a description of the relevant patents and their file histories, an introduction to the science that is necessary to understand the discussion that follows, and an outline of the procedural history of this litigation. The discussion section of the Opinion will address first the issue of obviousness and then the issue of inequitable conduct.

Background

A. Diabetes

Diabetes is a disease in which the body is unable to metabolize blood sugar or glucose derived from food, primarily carbohydrates, into energy efficiently. The

blood glucose level is essentially controlled by insulin, which drives the process whereby glucose enters the cells of the body and is turned into energy. Insulin is a hormone made by specialized cells within the pancreas called beta cells.

There are two types of diabetes. Type 1 diabetes is characterized by the fact that the pancreas does not produce insulin. Insulin must therefore be supplied from an external source, such as an injection or insulin pump. Type 1 diabetes compromises less than 10% of diabetes cases worldwide.

In Type 2 diabetes, the body fails to utilize effectively the insulin that is produced. This failure usually starts in the muscles, which collectively use most of the glucose produced by the body. The liver is also responsive to insulin, which instructs the liver when to stop making glucose. When the liver becomes insulin resistant, it resists those instructions and continues to create glucose. Insulin resistance also impacts the pancreas, at first by forcing it to produce more insulin than normal. Over time, the increased resistance to the action of insulin overwhelms the ability of the pancreas to produce sufficient insulin, and the symptoms of diabetes begin to appear. If Type 2 diabetes is left untreated, the demand for insulin from the pancreas can eventually lead the beta cells to become dysfunctional, a phenomenon known as "exhaustion" or "burn-out."

Diabetes can cause great damage to the body. Due to the toxic effects of high glucose on blood vessels,

patients with diabetes are predisposed to chronic complications such as kidney failure, blindness, leg ulcers and amputations, heart attacks, and strokes.

B. Treatments of Diabetes

Type 2 diabetes may be treated with lifestyle changes, such as weight loss, improved diet, and exercise. These steps are rarely sufficient. A substantial portion of patients ultimately need injections of insulin. Insulin is effective because insulin resistance in Type 2 patients is not complete-insulin may still lower blood glucose.

The past twenty-five years have seen the development of a number of oral antidiabetic drugs ("OAD") that are used instead of, or in conjunction with, insulin. Different classes of OADs have that have been developed work in the different parts of the body affected by diabetes. It is common practice to treat diabetes with a combination of several classes of drugs.

Sulphonylureas, which became available in the 1980s, are the oldest class of drug used to treat Type 2 diabetes, and work by stimulating the pancreas to secrete more insulin. Meglitinides work very much like the sulphonylureas but differ in that their onset is more rapid and their duration of action is briefer.[3] Biguanides

3. Alpha-glucosidase inhibitors, which are used infrequently in the United States, interfere with starch absorption in the intestine, thereby slowing the increase in blood glucose levels after meals.

help to reduce the liver's production of glucose. Metformin®, a biguanide, is frequently the first drug chosen to treat a newly diagnosed Type 2 diabetes patient. It became available in 1995.

The treatment of diabetes was revolutionized in the 1990's with the introduction of a class of drugs known as thiazolidinediones ("TZDs"). TZDs were first discovered by Takeda in the 1970s. They are peripheral insulin sensitizers, working within muscles to enhance the effect of insulin in that organ, and thereby to increase the muscles' ability to take glucose from the bloodstream.

The first TZD to be marketed in the United States was troglitazone, known by the commercial name Rezulin®. Rezulin®, which was developed by Pfizer, first became available in 1997. In May of 1999, two years after Rezulin® entered on the market, the Food and Drug Administration ("FDA") approved GlaxoSmithKline's Avandia® (whose active ingredient is rosiglitazone). The drug at issue here, ACTOS®, which was approved by the FDA in July of 1999, is the only other TZD currently approved by the FDA for sale in the United States.

In March 2000, Pfizer withdrew Rezulin® from the United States market due to significant concerns about its safety. After Rezulin® was withdrawn, ACTOS® and Avandia® essentially split the TZD market in the United States. More recently, research has shown that these two TZDs have a greater positive effect in the treatment of cardiovascular disease than other anti-diabetic drugs, and that ACTOS® in particular has a greater impact

than Avandia® on lowering cardiovascular risk.[4] Based in part on this research, there is evidence that ACTOS® is becoming the preferred TZD among knowledgeable doctors.

By any measure, ACTOS® has been a hugely successful commercial product. It has led the TZD market for new prescriptions written by endocrinologists since February 25, 2000. In October 2001, it became the seventh fastest product in pharmaceutical history to reach $1 billion in annual sales.

C. Takeda's Research into Diabetes

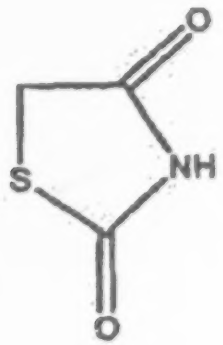
Takeda, a Japanese pharmaceutical company, is based in Osaka, Japan. Takeda North America is a wholly owned United States subsidiary of Takeda America Holdings, Inc., which is a wholly owned subsidiary of Takeda.

Takeda began its research into obesity and related diseases in the early 1960s. Working with Nagoya University in Japan, Takeda developed an animal model that exhibits the symptoms of diabetes: KKA^{y} mice. This is an obese strain of mice that consistently exhibits symptoms of insulin resistance under normal diet conditions. Takeda researchers also developed the

4. To reduce cardiovascular risk both trigylcerides and LDL-cholesterol should be lowered. Pioglitazone has shown better trigylceride lowering properties than rosiglitazone and also has shown less of an effect of raising LDL-cholesterol.

genetically obese and diabetic Wistar fatty rat. The development of the KKA^{y} mouse and the Wistar fatty rat were significant steps in the effort to develop pharmaceutical treatments for diabetes since compounds could now be tested in diabetic animals.

Takeda made a pharmacological breakthrough in the 1970s. Takeda researchers discovered the first TZD derivative compound and learned that TZDs exhibited considerable blood glucose lowering effects in KKA^{y} mice.[5] The defining characteristic of TZDs is the presence of a thiazolidinedione group at the right end or moiety[6] of a molecule. The chemical structure of this group is:



5. Takeda's diabetes research was conducted through a partnership of Dr. Yutaka Kawamatsu, who ran the chemical research into TZDs and Fujita, who oversaw the biological research.

6. A moiety is a "group of atoms forming a distinct part of a large molecule." *Oxford English Dictionary* (Draft Revision to 2d Ed. December 2003).

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Takeda's work with TZD derivatives revealed that at least some compounds within the TZD class did not lower blood glucose in normal, non-diabetic animals. This was another important finding because it suggested that TZD derivatives did not affect the level of insulin in the body, but instead were insulin sensitizers, a term for compounds that ameliorate insulin resistance, the defining characteristic of Type 2 diabetes.

While scientists did not initially understand how TZDs work, and still debate today precisely how TZDs actually function within the body, there is a growing consensus that TZDs enhance the signal of insulin receptors that reside in the cells that require or store energy, such as muscles and fat cells. When we eat, the level of glucose rises in the bloodstream, stimulating the pancreas to secrete more insulin. The insulin which is flowing through the blood binds to insulin receptors, causing changes inside cells that allow glucose to enter the cell from the bloodstream, where it can be burned for energy or stored. Because of a negative feedback system, as the level of glucose in the blood falls, the pancreas produces less insulin so that the blood glucose returns to normal levels.

TZDs activate the insulin receptors by binding to a molecule within the cell's nucleus known as PPAR-gamma. Together, they bind to specific areas on the cell's DNA, producing messenger RNA and effectively stimulating the production of glucose transporters within the cell. The transporters travel to the surface of the cell and facilitate the entry of glucose into the cell from the bloodstream.

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Scientists still do not fully understand how insulin resistance works at the cellular level, but it is believed that the problem relates to the interaction between the insulin receptors and that section of the DNA in the cell's nucleus that is responsible for triggering the production of glucose transporters. As noted, TZDs work by binding with a molecule in the nucleus of the cell called PPAR-gamma. When that happens, the PPAR-gamma molecule changes shape and binds to the DNA in the cell. Each TZD seems to bind differently with the PPAR-gamma. As a result, different TZDs have different metabolic effects. TZDs also bind with other PPAR molecules in the cell, such as the PPAR-alpha and PPAR-delta molecules, further contributing to the differences among TZDs.

The fact that TZDs affect the gene transcription process within DNA makes them both effective but also unpredictable. Only a fraction of the genes in the human body have been identified. It is possible that TZDs stimulate genes that are still unknown. As one of Takeda's expert endocrinologists has explained, gene transcription is "a big black box. . . . When you are stimulating a gene, you can do a lot of things downstream that you may not understand."

D. The Development of Ciglitazone and the '200 Patent

Takeda's research led to the synthesis of the TZD ciglitazone in February of 1978. Takeda worked for many years to develop ciglitazone, only abandoning it when it proved toxic during human clinical trials. Thereafter,

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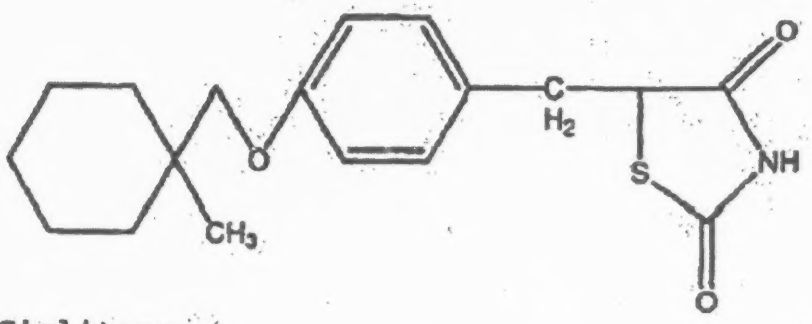
Takeda's search for a TZD to develop as a commercial pharmaceutical used ciglitazone as a benchmark. Takeda searched for a compound that was more potent than ciglitazone, which required unrealistically high doses to be effective, and yet non-toxic.

Ciglitazone's chemical structure is illustrated here:



Ciglitazone

It was identified as a particularly promising compound based on its blood glucose lowering effect in KKA^y mice. Based on this research, Takeda filed a United States patent application on July 27, 1979, covering a generic class of TZD derivatives including ciglitazone. The application eventually resulted in the issuance of U.S. Patent No. 4,287,200 (" '200 Patent").

The application for the '200 Patent (" '200 Application") made eight claims. Its first claim was its broadest and covered hundreds of millions of TZD compounds through a formula that allowed for a wide variety of chemical structures on the left-hand end to

be attached to the TZD structure on the right. The '200 Application represented that TZDs are "novel compounds and useful as, for example, remedies for diabetes, hyperlipemia and so on of mammals including human beings."

The '200 Application was the subject of two office actions by the PTO. The second office action allowed two of the eight claims, but rejected all of the other claims as containing "improper Markush groups." *See Ex parte Markush*, 1925 CD 126, 340 Off. Gaz. Pat. Office 839 (Comm'r.Pat.1925).[7] The office action identified three separate groups the patent examiner believed were contained in the '200 Application.[8]

In response to the second office action, Takeda amended its application to cover only the first of the three groups identified by the examiner. In the

7. The examiner cited a recent appellate decision, *In re Harnisch*, 631 F.2d 716 (C.C.P.A.1980), as providing a legal basis for the rejection. *Harnisch* confirmed the concept of an "improper Markush group" as a basis for rejecting a patent application. *Id.* at 721. The decision explained that the issue underlying improper "Markush groups" was better described as a lack of "unity of invention." *Id.*

8. The three groups identified were distinguished by the possible structures on the left end moiety. Group A was composed of compounds where the left end moiety contained an alkyl, cycloalkyl or phenylalkyl; for Group B the left end contained a thienyl or furyl; for Group C the left end contained a pyridyl or thiazolyl. It is this last group that is of importance here; pioglitazone is a left end pyridyl.

amendment Takeda noted that it might file "divisional applications" to cover the other groups.

The '200 Patent was issued on September 1, 1981. Fujita and Dr. Yutaka Kawamatsu were named as co-inventors. In addition to the generic class of TZDs, the patent also presented, as examples, sixty specific compounds covered by the generic formula. Included among those disclosed was compound 42, whose left end was a 2-pyridyl ring with a methyl at the 6-position. Compound 42 is a compound of importance to this litigation and is discussed in detail below.[9] Like ciglitazone, compound 42 had first been synthesized in 1978.

E. Two Divisional Patents

Takeda obtained two divisional patents for the '200 Patent. First, through a patent issued on July 20, 1982, as U.S. Patent No. 4,340,605 (" '605 Patent"), Takeda received a patent for the third group identified by the examiner.[10] In support of the application for that patent, Takeda presented a declaration from Fujita providing data for blood glucose and lipid lowering effects of twelve compounds tested in KKA^{y} Mice, including compound 42 from the '200 Application.

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9. Compound 42 from the '200 Patent is compound (b) from the '777 Patent.

10. The third group identified, compounds with a pyridyl or thiazoyl on the left end, had been designated group C by the examiner.

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On July 7, 1982, Takeda filed an application for a second divisional to the '200 Patent. The patent, which issued on March 20, 1984, as U.S. Patent 4,438,141 (" '141 Patent"), covered the second grouping that was identified by the examiner in the course of prosecuting the '200 Patent.

F. Sohda II

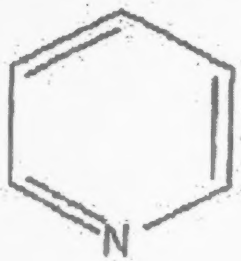
While it was securing the '200 Patent, Takeda continued its research into TZD derivatives and by early 1982 had evaluated approximately 1000 compounds for their potential as antidiabetic agents. Important information about TZDs and Takeda's research efforts was published in a series of articles by Takeda's scientists. Of particular importance to this Opinion, because it constitutes prior art for the '777 Patent, was an article received for publication on April 22, 1982, T. Sohda et al., *Studies on Antidiabetic Agents. II. Synthesis of 5-[4-(1-Methylcyclohexylmethoxy-benzyl]) thiazolidine-2,4-dione (ADD-3878) and its Derivatives,* Chem. Pharm. Bull., 30:3580-3600 (1982) ("Sohda II"). Sohda II did not disclose pioglitazone, but it did disclose a compound that was structurally close to pioglitazone, and which Alphapharm contends made the invention of pioglitazone obvious.

Sohda II described 101 specific TZD compounds, giving data on each compound's efficacy. As was the case in the Fujita declaration submitted in the prosecution of the '605 Patent, the data were presented as a score ranging from one to four in two categories: hypoglycemic

activity (blood sugar lowering activity) and plasma triglyceride lowering activity. A higher score represented greater potency.

While the article did not present data on the toxicity or side effects of the compounds, it did comment on these issues for particular compounds. Of the 101 compounds, the article identified three compounds-compounds 47, 49 and 59-as showing the most favorable profiles "in terms of activity and toxicity." The article concluded that those three compounds "may be valuable for the treatment of maturity-onset diabetes and/or hyperlipidemia which involves obesity." Compound 49 was ciglitazone and compound 47 was a compound whose left end was structurally similar to ciglitazone's. The left end of compound 59 was different from 47 and 49, its left end terminated with a 3-pyridyl ring.

Since pioglitazone has a pyridyl ring at its left end, it is important to discuss compound 59 and related compounds described in Sohda II in some detail. To begin with, the term pyridine refers to a six-membered carbon-containing ring with one carbon replaced by a nitrogen. A pyridyl ring is diagramed as follows:



Pyridine

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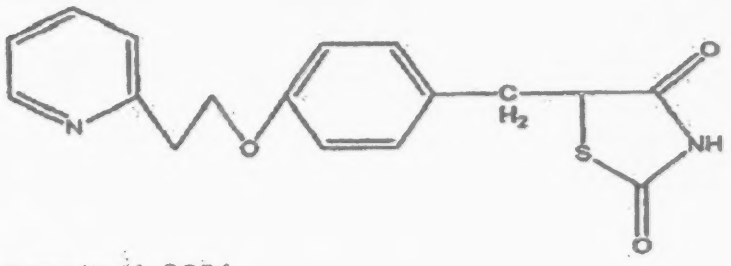
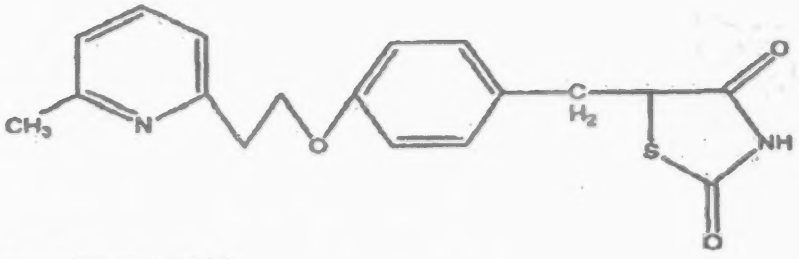
The numbering on a ring begins with the highest atomic weight atom in the ring, which in this case is nitrogen. The numbering moves in a counterclockwise fashion. As noted, compound 59 was a 3-pyridyl ring, which means that the ring is attached at the third position to the rest of the molecule.

The article disclosed two 2-pyridyl compounds: compound 57, the unsubstituted 2-pyridyl, and compound 58, the 6-methyl substituted 2-pyridyl. The term unsubstituted indicates that the pyridyl ring does not have any substituents (such as a methyl or ethyl group) linked to it, while the term 6-methyl indicates that a methyl is linked to the ring at the 6 position, using the numbering system described above. Diagrams of the two compounds are presented below:



Compound 3894



Compound 3959
Compound (b)

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Compound 57 from Sohda II was designated by Takeda as Compound 3894 ("Compound 3894"), and compound 58 was designated Compound 3959 ("Compound 3959") and identified in the '777 Patent as compound (b). The defendants' challenges to the '777 Patent largely hinge on assertions concerning these two compounds, and they will generally be referred to as compounds 3894 and (b) in the course of this Opinion.[11]

The 101 compounds described by Sohda II were organized into seven groups. The article commented on characteristics associated with compounds in each of the seven groups. When discussing the group into which compounds 57 and 58 fell, it noted that "[a]lthough compounds 56, 57, 58, 59 and 63 . . . showed potent activities, they, *especially 57 and 58,* caused considerable increases in body weight and brown fat weight," in the rodents in which they were tested. (Emphasis supplied.)

In the 1980's, scientists believed, as they do today, that increases in body weight are not desirable for diabetics. There was disagreement, however, about the implications of an increase in brown fat in rodents for humans treated with the same compound. Adult humans have relatively little brown (as opposed to white) fat, while rodents carry a significant amount of brown fat in the saddle between their scapulas. Brown fat has a

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11. As already noted, compound (b) had previously been disclosed by Takeda as compound 42 in the '200 Patent, and was also one of the twelve compounds later listed in the Fujita declaration that accompanied an amendment to the application for the '605 Patent.

thermogenetic effect, generating heat to keep them warm. At the time that Sohda II was written, overall weight and fat gain caused by pharmaceuticals were thought to correlate in mammals, including rodents and humans.

G. The Third Divisional Patent: The '779 Patent

On March 15, 1983, Takeda filed a third divisional patent to the '200 Patent. The application sought to expand the grouping of compounds originally covered by the '605 Patent, by adding compounds where "the pyridyl or thiazolyl groups may be substituted."[12] A preliminary amendment also noted that compounds in which "hetrocyclic rings are substituted have become particularly important, especially Compound 42 in example 9." Compound 42 was the compound destined to be used as a comparator in the '777 Patent, where it is listed as compound (b).

Because the application only sought to expand the groups covered by the '605 Patent but not to introduce a substantively different claim, Takeda filed a terminal disclaimer, noting that the "inventive entity" covered by the '605 Patent and the application were the same, and thereby disclaiming any protection of the compounds in this application beyond the expiration of the '605 Patent. The application was approved by the PTO and issued on April 24, 1984, as U.S. Patent No. 4,444,779 (" '779 Patent").

12. A thiazolyl is a five member heterocycle, with a nitrogen and sulfur at positions 1 and 3, respectively.

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H. The '902 Patent

Takeda's patent prosecutions were not limited to the divisionals of the '200 Patent. On December 29, 1982, Takeda filed an application covering TZD derivatives with a cyclohexane ring on the left end.[13] The patent issued on July 24, 1984 as U.S. Patent 4,461,902 (" '902 Patent").

I. The Failure of Ciglitazone

After Takeda's TZD development program attracted the interest of Upjohn, Takeda and Upjohn worked together on the development of ciglitazone from 1981 to 1983. Both companies analyzed the compound's anti-diabetic properties and toxicity, and based on those studies, began Phase I safety studies with human volunteers in both the U.S. and Japan.

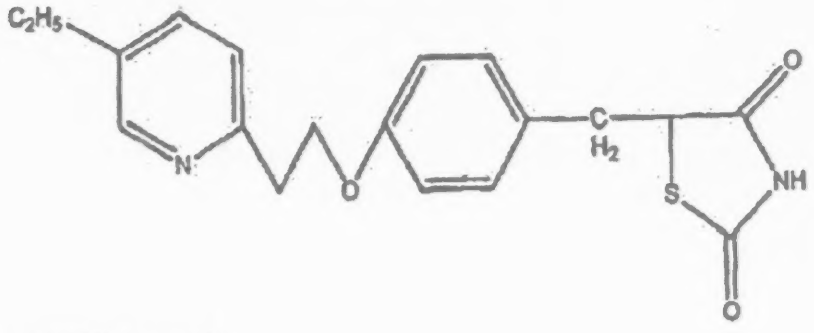
As work on the development of ciglitazone progressed it became evident that the compound could not be successful as a commercial anti-diabetic. In November 1982, it was determined that ciglitazone caused cataracts in rats that were being treated with the compound as part of a ninety-day toxicology study. Upjohn believed that the FDA would block a compound that caused cataracts from the U.S. market. Second, a clinical trial in Japan suggested that ciglitazone might not be effective for a Type 2 diabetic patient unless the

13. A cyclohexane ring is a saturated ring of six carbons. Ciglitazone's left moiety contains a cyclohexane ring.

dose was above 500 milligrams per day, a dosage which was impractical. By 1983, Takeda and Upjohn renewed their search for a more potent, non-toxic compound.

J. Initial Development of Pioglitazone

Meanwhile, Fujita was working with Dr. Kanji Meguro ("Meguro"), the Chief Scientist of the Chemical Research Laboratory at Takeda, to develop ideas for new compounds to be synthesized and tested. On September 7, 1982, pioglitazone was synthesized. It terminates at its left end in a 2-pyridyl ring with an ethyl at the 5 position on that ring.[14] It was given the internal Takeda compound number 4833.



Pioglitazone
Compound 4833

14. An ethyl group is C_2H_5. Ethyl groups differs from methyl groups, CH_3, by a single CH_2 group. Ethyl and methyl are both lower alkyls.

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The first screening of pioglitazone for efficacy in November 1982 noted its promise:

> Initial Screening
>
> 10 Samples were tested in KKA^{y} mice. 2 samples were significant in lowering blood glucose. The effect of AD-4833 was relatively strong, 0.005% food admixture 4-day administration resulted in reducing blood glucose, plasma TG and NEFA by 46%, 31% and 30% respectively. No significant increase in body weight was observed. The effect was weaker than that of ADD-3959 [identified as compound (b) in the '777 Patent].[15]

Takeda scientists also conducted preliminary toxicity tests on compounds that showed promise. Pioglitazone was the least toxic of all the TZD compounds evaluated in 1983 and 1984.

Following the failure of ciglitazone, Upjohn and Takeda renewed their collaborative research. In their search for a new compound they focused on the 130 TZD derivatives that had been tested during the ciglitazone selection process, but also synthesized some new compounds.

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15. Takeda seems to have used both AD- and ADD- as prefixes when designating compounds during their research. No explanation has been given for any difference between the two prefixes. This Opinion does not use either designation.

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The decision by Takeda and Upjohn to continue to research TZD derivatives went against some of the thinking in the industry. Other leaders in the diabetes field believed that better avenues for research included developing insulin secretagogues (compounds which combat insulin resistance by causing the pancreas to create more insulin) and treatments for late-stage consequences of Type 2 diabetes, such as neuropathy, nephropathy, and retinopathy.

One of the compounds that was retested during this period was compound (b). Compound (b) had shown strong blood glucose lowering activity in mice and triglyceride lowering activity in both mice and rats. Despite its efficacy, compound (b) was dropped from consideration when testing revealed significant toxicity to the liver and heart as well as a decrease in the number of erythrocytes, a sign of potential toxicity to bone marrow. Compound (b) also failed the cataract screening test conducted by Upjohn.

Based on the experiences with ciglitazone and compound (b), Takeda made identifying a compound without toxic effects its highest priority. It was Upjohn's view that any compound that failed the in vitro chick lens assay test for cataractogenesis had to be ruled out from consideration for development.

K. Takeda's Testing Methods

Takeda conducted many efficacy tests on numerous compounds, including pioglitazone, throughout 1983 and

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1984. In order to screen for efficacy, KKA^{y} mice or rats were treated with different dosage levels of a compound for four days. Initial tests usually involved just two doses of the compound to determine roughly if the compound was active. The dosage levels were calculated as milligrams of compound per kilogram of body weight of the treated animal per day (mg/kg/day). The researchers typically matched the animals to be tested by age, sex and body weight. From the pools of animals, groups of five animals were randomly chosen for each dosage level in the test and a separate group of five was chosen to serve as a control. On the fifth day of the screening, the blood glucose and triglyceride levels of the test animals were measured and were compared to blood taken from untreated control animals.

For many compounds Takeda also conducted three dose efficacy tests, to assist researchers in determining the dosage of a compound necessary to reduce an animal's blood glucose level or triglyceride level by 25%. The effective dose required to reduce the levels by 25% is called the "ED"[25].

Takeda's experiments were performed by technicians. At the end of a three dose efficacy test, the technician would perform regression calculations to plot the best straight line between the three data points. The results would then be reviewed by a trained scientist or by Fujita in order to determine whether the points plotted or the line determined by the regression equation actually corresponded as well as it should to a true dose response curve.

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The relationships between two variables in biological systems, such as the changes in blood glucose concentrations with a change in a dosage of a drug, are usually not linear but rather exponential. Plotting the change of the one variable against the other will often result in a curve which is made linear through the application of a process called linear regression. There are limitations, however, on the reliability of a linear regression. A linear regression is more reliable if the interval between the data points is limited. It is significantly less reliable when the administered dosages do not fall within the effective dosage range of the compound being tested since including even one data point that is outside of the linear response region can significantly change the relationship between the three points plotted in a three-dose test. Extending a line beyond a data point to reach an ED^{25} value that was not within the tested range also runs a considerable risk that the projected results will be unreliable.

Takeda was testing new compounds whose properties were unknown and it had to guess what the best dosage range for testing might be. Not infrequently, it chose dosages that were above or below the effective dosage range. This meant that Takeda often had to conduct several experiments to improve its understanding of the effective dosage range of a compound. In addition to the challenges of making an accurate determination of the ED^{25} values, Takeda scientists also had to monitor the experiments for other possible factors that might make a particular experiment's results unreliable.

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L. Report A-15-13

On February 8, 1984, Takeda forwarded a copy of Fujita's report A-15-13 ("Report A-15-13") to Upjohn. The report, which was titled "Preliminary Studies on Toxicological Effects of Ciglitazone-Related Compounds in the Rats", disclosed the results of preliminary toxicity studies conducted on fourteen compounds that Takeda had considered as candidates for development. The report detailed the method of testing that had been employed: oral doses of 100mg/kg/day of the test compound for two weeks given to five to six week old male and female Wistar rats. At the end of the testing period the rats were sacrificed, body weights and organ weights were analyzed, as were blood chemistry and hematology. The report contained the organ weight expressed as normalized weight (calculated by dividing the organ's weight by the weight of the rat and expressing the weight as a percentage) in order to compensate for the fact that animals differ in size. Pioglitazone was one of the compounds presented in Report A-15-13 and showed no statistically significant toxicity.

In addition to pioglitazone, several other compounds of interest to this Opinion were among the fourteen, including the unsubstituted 2-pyridyl (compound 3894) and the 5-methyl 2-pyridyl (compound (c) as designated in the '777 Patent). The introduction to the report noted that each of these three compounds was less toxic "in regard to reduction of blood red (sic) cells and hypertrophy of liver and heart which were common toxic

effects in ciglitazone-related compounds." It added, "[c]onsidering the fact" that compound 3894, pioglitazone and compound (c) "are five times as potent as ciglitazone in the pharmacological activities, they appear to be much easier to continue further studies including clinical trials." In point of fact, however, the report found that compound 3894 produced a statistically significant negative effect on the heart of male rats and that compound (c) had such an impact on platelets. Two other compounds that were used as comparators in the '777 Patent also demonstrated toxicity. Compound (b) was toxic to the liver, heart and erythrocytes, among others things, while compound (d) was toxic to the liver and heart.

M. March 1984 Plan

After two days of meetings between Takeda and Upjohn in March 1984, at Upjohn's headquarters in Kalamazoo, Michigan, the participants agreed that Takeda would select fifty TZD compounds based on hypoglycemic activity in both the KKA^{y} mouse and the Wistar-fatty rat. Upjohn was to test the leads identified by Takeda in the in vitro chick lens assay for cataractogenic activity, and Takeda was responsible for other toxicity testing.[16] Takeda had already provided Upjohn with KKA^{y} mice so that Upjohn could replicate Takeda's efficacy testing. It also gave Upjohn the fifty compounds that it had synthesized and selected for this intensive review.

16. Takeda was to carrying out two-week toxicity studies for the leads in Wistar rats at 100 mg/kg/day.

The minutes of the March meeting reflect that it was "desirable that leads selected for further development are clean" in the chick lens assay. Based on a combination of the chick lens assay and the toxicity studies, nine to ten leads were expected to emerge and be subject to further testing by Takeda and Upjohn. It was anticipated that four to five leads would emerge from that further testing and proceed to ninety-day toxicity studies in both rats and dogs. Compounds which emerged as "clean" through all of the stages of testing would be "considered for further development with a goal of IND filing for the best compound as a drug candidate."[17] The minutes established a time line for each stage in the process. The next meeting, for selection of the nine to ten leads was scheduled for August 1984.

In selecting the fifty compounds, Takeda was also to consider the "uniqueness of chemical structure." The emphasis on the uniqueness of the chemical structure as a criterion for selecting the initial fifty compounds arose from a Takeda policy that candidate compounds should be reasonably unique from each other in their chemical structures because toxicological problems and adverse reactions are often caused by discrete chemical structures. By emphasizing variety in the chemical structures to be studied, Takeda hoped to avoid losing entire ranges of candidates due to a particular

17. An Investigational New Drug Application ("IND") is an application filed with the FDA to conduct clinical trials (i.e. tests on humans). *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, __, 125 S.Ct. 2372, 2377, 162 L.Ed.2d 160 (2005).

structure's toxicity.[18] Based on those same concerns, Upjohn researchers endorsed the decision to make chemical uniqueness a selection criterion.

The fifty compounds chosen by Takeda were a mix of those that had already been tested in earlier research and those that Takeda had recently synthesized. Among the recently synthesized compounds were three that appeared as comparators in the '777 Patent: compounds (c), (d), and (e), which were first synthesized on July 21, May 4, and August 4, 1983, respectively. Because Takeda had observed that pioglitazone was comparatively potent and exhibited no toxicity it synthesized compounds that were structurally related so that it could compare the results.

Takeda's benchmark for efficacy was the ED^{25} of ciglitazone. The candidate compounds were continually evaluated from July through October of 1984 in order to find what Takeda scientists considered the most reliable ED^{25} values.

N. October 30, 1984 Meeting and Report A-15-34

Obtaining the efficacy and toxicity data for the candidate compounds turned out to be much more

18. While Mylan argued that Takeda and Upjohn were concerned in 1984 not with identifying the best anti-diabetic treatment but with the patentability of a compound, the Takeda and Upjohn witnesses presented entirely credible testimony that they were driven by concerns about efficacy and safety. After all, a patent on a useless compound is useless.

complicated and time consuming than expected. The meeting with Upjohn originally planned for August 1984 did not take place until the end of October. At the meeting Takeda presented Fujita's report A-15-34, which was titled "Pharmacological and Toxicological Studies of Ciglitazone and its Analogues" ("Report A-15-34"). This report is of critical importance to the issues of inequitable conduct raised by defendant Mylan.

Report A-15-34 lists fifty compounds in Table 1. The report gives the chemical structure of each compound as well as efficacy and toxicity data. In generating the report, Fujita examined all of the test results to locate the most reliable ED^{25} numbers for each compound. In addition to listing the ED^{25} score which he considered to be the most reliable for each compound, Fujita also indicated in a parenthetical the relative efficacy of each compound to that of ciglitazone. For instance, the benchmark for all testing, ciglitazone, was listed first with an ED^{25} for glucose lowering in KKA^{y} mice of "40 (1)". Pioglitazone was listed about one-third of the way down the table with an ED^{25} of "6 (6.7)", indicating that a dose of 6 mg (per kg per day) of pioglitazone achieved an ED^{25}, rendering it about 6.7 times more potent than ciglitazone, which required a dose of 40 mg to achieve that result. The parenthetical sometimes indicated the range of the test results obtained by Takeda.

Table 1 also indicated the results of the in vitro chick lens assays conducted by Upjohn. A compound failed the chick lens assay if it caused a change in pH or a cloudy appearance at a lower concentration than did ciglitazone.

Finally, the report provided summary data for hepatomegaly (liver toxicity), cardiomegaly (heart toxicity) and anemia (erythrocyte depletion) from two-week toxicology studies in male and female Wistar rats. The data were presented using a rating system based on the degree of toxicity. For liver and heart, toxicity was evaluated by a percentage gain in weight; for anemia, toxicity was evaluated by a percentage decrease of erythrocytes. Rather than give precise toxicity numbers, the report listed three ranges of toxicity in terms of growth or decline: 8-20%, 21-25%, and 26% and above.

Fujita selected twelve of the fifty compounds as compounds on which the meeting participants should particularly focus their attention, and presented the data for these twelve on Table 2 in the report. In selecting the twelve, Fujita considered the potency of a compound in comparison to its performance in toxicity testing, including the chick lens assay tests, as well as the structural diversity of the compounds. Fujita selected only two compounds whose left end was a pyridyl ring. One of those two was pioglitazone. Pioglitazone was the only compound among the twelve that showed no toxicity, although many of the others listed on Table 2 were far more potent. None of the comparator compounds from the '777 Patent appear on Table 2, although all of them appear on Table 1 of Report A-15-34.

During the meeting, the scientists from Takeda and Upjohn reviewed the data for all the compounds presented in Table 1, giving particular attention to the

twelve compounds on Table 2. The discussion was an open one and Upjohn was free to suggest that any compound from Table 1 be considered for selection as a lead.

At the meeting, Upjohn conveyed its view that low toxicity was far more important than extreme potency. Upjohn urged that the most important criterion for selection was the therapeutic ratio, that is, the difference between the effectiveness of the drug and the appearance of side effects. Due to its lack of toxicity, Upjohn pressed for the selection of pioglitazone over far more potent compounds.

In the end, Takeda and Upjohn selected five compounds from Table 2 for further testing. Pioglitazone was among the five. None of the other four ended in a pyridyl ring, and none of the others emerged as a viable candidate for commercial development from the additional testing which followed.

The decisions reached at the October meeting were vitally important to both Takeda and Upjohn. Each company intended to spend millions of dollars and valuable research resources on the selected compounds. In addition, their scientists would be spending several years of their professional lives developing the chosen compound. Having experienced a significant set back with the failure of ciglitazone, Upjohn and Takeda were looking for a compound that would validate both their focus on TZDs and their use of the KKA^y mouse as an effective way to test the efficacy of compounds intended

to treat diabetes. Development of a safe and efficacious molecule that could be successfully developed as a pharmaceutical would validate the years Takeda and Upjohn had invested in research.

O. Final Selection of Pioglitazone

Takeda and Upjohn continued their evaluation of the candidate compounds in late 1985 and early 1986. After more extensive toxicity studies, pioglitazone was chosen as the primary candidate for commercial development at a meeting between Upjohn and Takeda in Osaka on March 7, 1986. Pioglitazone met the important toxicity criteria: it was clean at 100 mg/kg/day in heart, liver and erythrocyte toxicity screening, as well as in the in vitro chick lens assay. Upjohn repeatedly confirmed pioglitazone's ED^{25} score.

Upjohn's decision to develop pioglitazone was not based on Takeda's data alone. Upjohn, under Colca's supervision, had conducted confirmatory efficacy and toxicity tests on over fifty of the TZD derivatives for which it received data from Takeda, including ciglitazone and pioglitazone, following experimental protocols identical to those described by Takeda in Report A-15-34. Upjohn's tests did not produce any results that were materially inconsistent with those reported to it by Takeda.

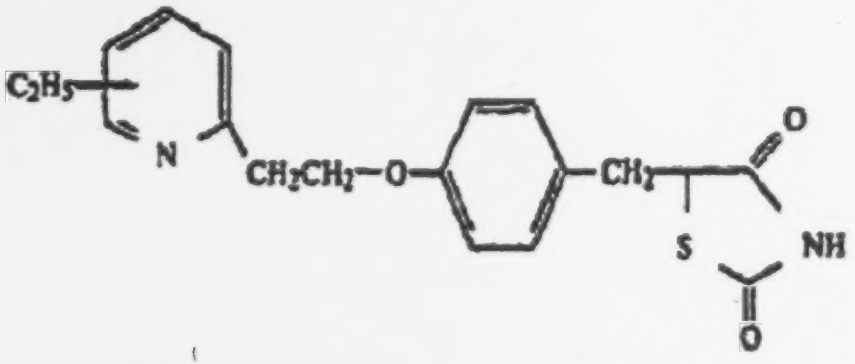
Appendix B

P. Prosecution History of the '777 Patent

In December 1984, Meguro submitted a request to file a patent application to Takeda's Central Research Library. The request, dated December 17, 1984, names Meguro and Fujita as joint inventors and identifies the structure of pioglitazone. The internal patent request only claims pioglitazone; there is no request to claim an ethyl substituent at any other position on the pyridyl ring.

On January 19, 1985, Takeda filed a Japanese priority patent application covering pioglitazone, and containing the efficacy and toxicity data presented in Table 1 of the '777 Patent. On January 17, 1986, Takeda filed the U.S. patent application covering pioglitazone. The substance of the application was virtually identical to the Japanese priority patent application. The patent application included an Information Disclosure Statement ("IDS") which identified relevant prior art references as including the '200 Patent and Sohda II.

Takeda made six claims in its application. Claim 1 was for a compound of the formula:



or a pharmacologically acceptable salt thereof.

Appendix B

The right end of the molecule is the defining TZD structure. For our purposes, the critical part of the formula was the left-hand portion, which was the pyridyl ring with a C_2H_5 (or ethyl group) connected to the pyridyl ring by a line leading into the middle of the ring. Drawing a line into the center of the ring means that the ethyl group can be located on any open position on the pyridyl ring.

Claims 2, 3 and 4 are dependent claims which refer back to claim 1.[19] Claim 2 is for the compound in claim 1 with the ethyl group in the 5 position, that is, pioglitazone. Claim 3 is for the sodium salt of pioglitazone. Claim 4 is for the compound in claim 1 with the ethyl group in the 6 position. This compound has never been developed by Takeda.

Takeda's application states that the purpose of its invention "is to provide compounds which can be practically used as antidiabetic agents having a broad safety margin between pharmacological effect and toxicity or unfavorable side reactions." In support of its statement, Takeda provided efficacy and toxicity data on six compounds. The toxicity data are identical to the data presented in Report A-15-13. The efficacy data are identical to that contained in Report A-15-34.

The six compounds listed in the table are identified as (I), (a), (b), (c), (d), and (e). Compound (I) is

19. The application also included two claims that were later withdrawn.

pioglitazone. Compound (a) is ciglitazone, which has a different left end moiety than that in the other five compounds identified in the table. Ciglitazone has a methylcyclohexyl ring instead of a 2-pyridyl ring. Ciglitazone was disclosed in the prior art, having been specifically identified in both the '200 Patent and Sohda II.

Compounds (b), (c), (d), and (e) and pioglitazone each have a 2-pyridyl ring at the left end. Compounds (b), (c), (d), and (e) have a methyl at the 6, 5, 4, and 3 positions, respectively, on the 2-pyridyl ring. Pioglitazone has an ethyl at the 5 position. Compound (b) was also specifically identified in both the '200 Patent and Sohda II.[20] Compound. (c), which has the methyl in the 6 position, is the homolog of pioglitazone.[21] Table 1 of the '777 Patent is reproduced below:

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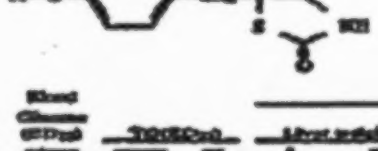
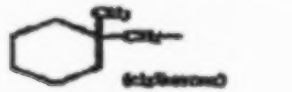
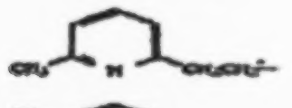
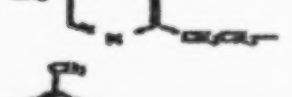
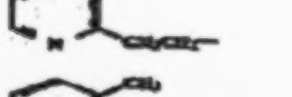
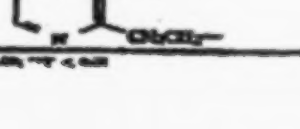
20. As has been noted previously, compound (b) was compound 42 from the '200 Patent and compound 58 from Sohda II.

21. The term homolog describes the relationship between two compounds that differ by the addition of a repeating group, usually a single CH_2 group. An ethyl group, C_2H_5, differs from a methyl, CH_3, by a single CH_2 group.

TABLE I



	Compound A	Blood Glucose (ED_{50}) g/kg	Tolbutamide		Therapeutic potency (a, B)					
					Liver uptake		Pancreas uptake		number of synthesis	
					A	B	A	B	A	B
(1)		4	6	3	−0.7	−3.5	+0.1	−3.9	−3.6	−0.7
(2)		40	40	20	+4.4*	+20.0**	+12.0*	+4.0	+3.0	−0.3
(3)		4	3	3	+3.5	+22.7**	+15.5**	+77.5**	−2.3	−6.5**
(4)		20	20	—	+1.3	−1.2	+7.2	+3.0	−4.3	−4.0
(5)		20	20	—	+3.5*	+6.0**	+3.3	+7.5*	−3.7	−3.3
(6)		10	20	—	−2.3	+6.0**	+17.3	+6.5*	−5.7*	−7.0**

*p < 0.05; **p < 0.01

Appendix B

Comparative data on compound (b) were included in Table 1 of the patent application because it is the closest prior art. Data on ciglitazone were included, despite its clinical failures, because it was the first TZD evaluated by Takeda to show potential for use as an anti-diabetic compound and had served as an index against which to compare new compounds. The application included data on the 3, 4 and 5-methyl variants of compound (b) because the compounds were structurally close to both pioglitazone and compound (b). They were also included to emphasize that the results for pioglitazone reported in Table 1 were "quite unexpected" even when compared to its homolog, compound (c).

Two errors were made in the section which describes the method by which Takeda tested for toxicity in rats. First, the application indicates that data on toxicity were obtained using Sprague-Dawley rats, when in fact the data were obtained from Wistar rats. Both are normal strains of rats and the same methods are used to test for toxicity in either strain. The error had no implications for the validity of the test results. In previous toxicology screens, the results of studies with the two species had been comparable.

The second error involved the age of the rats used in the testing. In the patent application, the age of the rats is listed as 5 weeks old when it should have been listed as 5-6 weeks old. In the two-week toxicity tests reported in Table 1 of the '777 Patent, the results for pioglitazone were obtained from rats that were six weeks old at the beginning of the two week test; the results for

the other compounds were obtained from rats that were five weeks old at the beginning of the two-week experiments. The data for all the compounds were normalized to body weight to account for variation in the size of the animals, and in each test the age of rats in the control group was the same as in the group receiving the compound. The one week age difference between the five and six week old rats did not affect the validity of the comparison.

On July 1, 1986, the examiner in charge of Takeda's U.S. patent application issued an office action ("Office Action") requesting an explanation of how to interpret the data presented in Table 1, particularly how to "balance the need for effective ED^{25} versus the need for lower toxicity." He rejected claims 1-5 under 35 U.S.C. § 112, quoting the section as follows:

> The specification shall contain a written description of the invention and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The Office Action also noted that Table 1 failed "to provide values for the control group." As a result of the lack of guidance on how to read the table, the Office Action pointed out that "one of ordinary skill is not

taught how to interpret the data and distinguish over the prior art." The Office Action requested guidance on whether there was a "therapeutic ratio" that could be used to compare the compounds and whether there was a threshold of "maximum toxicity." The Office Action concluded by asking "at what point is increased potency not desirable over increased toxicity? From the data provided one cannot conclude that [pioglitazone] is unexpectedly different from the rest."[22]

In response to the Office Action, Takeda submitted an amendment ("Amendment") and a declaration from Fujita ("Declaration"). The Amendment explained how to read Table 1, noting that the compounds (c), (d), and (e) were not disclosed in the prior art, but were tested because their chemical structure is similar to pioglitazone's. The Amendment explained how the ED^{25} values were calculated and the significance of the two-week toxicity testing in rats. It noted that only pioglitazone and compound (c) did not show any toxicity at a dose of 100 mg/kg/day for two weeks.[23] The Amendment calculated a "safety margin" for the different compounds, dividing the lowest toxic dose by the minimum effective dose. Noting that a compound

22. The file history for the '777 Patent reflects that three examiners, each of whom was trained in chemistry, were involved in the prosecution. Their annotations to Sohda II and Table 1 show particular attention to prior art compound (b).

23. As previously noted, pioglitazone and compound (c) are the only compounds in Table 1 with substituents at position 5 on the 2-pyridyl ring.

with a higher safety margin is preferable, it argued that the test results showed that pioglitazone was "the most advantageous." The Amendment also explained why it was "meaningless to show the values of the control" if one is skilled in the art.

In order to complete the safety margin calculations, Fujita's Declaration added calculations for rat triglyceride ED^{25} values for three compounds. These values were the only omissions in the columns of data presented in Table 1. Fujita asked his researchers to perform the experiments to generate the missing triglyceride ED^{25} data for compounds (c), (d), and (e). The report from the researchers who conducted the experiments showed ED^{25} data for two of the compounds but reported that compound (d) showed no effect. Fujita chose to take the ED^{25} rat triglyceride data for the third compound from Report A-15-34.

The experiments for rat triglyceride values for compounds (c) and (e) were performed by an experienced technician and supervised by an experienced researcher. During the experiment, the supervisor decided to exclude a control rat from consideration. It was common at Takeda to give researchers discretion not to use data from a single outlier animal.

Takeda filed its Amendment and the accompanying Declaration from Fujita with the PTO in November 1986. The PTO issued a Notice of Allowability on January 6, 1987. The patent issued on August 18, 1987. The '777 Patent was originally set to expire on January 17, 2006.

The patent term was extended by five years to January 17, 2011, pursuant to a petition filed by Takeda under the Hatch-Waxman Act.

Q. Upjohn Abandons Pioglitazone

Upjohn ended its collaboration with Takeda in September of 1993. In doing so, Upjohn considered an upcoming "milestone" payment due to Takeda, its desire to leave the diabetes market, and its concern about litigation risks associated with launching a new drug. Upjohn management also had concerns about some of the results from longer term toxicity studies on pioglitazone. The Upjohn scientists most directly involved in supervising the development of pioglitazone disagreed with the decision and were deeply disappointed by it. Upjohn's decision contributed to the long delay between the '777 Patent issuing and the FDA approving ACTOS®, a delay which resulted in pioglitazone being the third TZD, instead of the first, to reach the U.S. market.

R. Combination Uses

Takeda has received seven patents for pioglitazone to be used in combination with other drugs ("Combination Use Patents"). All but one of the Combination Use Patents expire on June 16, 2016; one expires on August 9, 2016. As already noted, it is common for diabetics to be treated with several drugs at the same time, each targeting a different body mechanism associated with the disease.

Appendix B

S. Marketing ACTOS®

The FDA approved ACTOS® in July 1999. Before May 1998, Takeda had no wholly owned United States sales entity. Takeda North America was created in May 1998 to market ACTOS® in the United States. In preparation for the launch of ACTOS®, Takeda Pharmaceuticals America, Inc. ("TPA"), the predecessor to Takeda North America, entered into a license agreement with Takeda which would allow Takeda North America to sell and market ACTOS® in the United States. TPA also entered into an agreement on December 14, 1998 with Eli Lilly and Company, which required Eli Lilly to co-promote ACTOS® with Takeda North America.

T. Hatch-Waxman Act[24]

The introduction of new drugs in the U.S. market is governed by the Federal Food, Drug and Cosmetic Act, which prohibits the introduction into interstate commerce of "any new drug, unless an approval of an application filed pursuant to subsection (b)" of 21 U.S.C. § 355 "is effective with respect to such drug." 21 U.S.C. § 355(a). Subsection (b) describes the process of filing a New Drug Application ("NDA") with the FDA. The process of filing an NDA is typically costly and time-consuming. In the case of pioglitazone, for example, it took almost 12 years from the issuance of the '777 Patent

24. This treatment of the Hatch Waxman Act draws significantly from the description in *In re Tamoxifen Citrate Antitrust Litig.*, 429 F.3d 370, 374-77 (2d Cir.2005).

until pioglitazone (in the form of pioglitazone hydrochloride) was approved by the FDA for the treatment of Type 2 diabetes on July 15, 1999.

In 1984, in order to accelerate the approval process for low-cost generic versions of established drugs, Congress enacted the Hatch-Waxman Act. Among other things, the Hatch-Waxman Act added subsection (j) to Section 355. Hatch-Waxman Act § 101. Subsection (j) provides for the filing of an Abbreviated New Drug Application ("ANDA") with the FDA for the bioequivalent form of a drug already approved for safety and effectiveness. 21 U.S.C. § 355(j)(1), (j)(2)(A), (j)(7)(A). Subsection (j)(7)(A) further provides that the Secretary of the FDA will create and maintain a list of such approved drugs. *Id.* § 355(j)(7)(A). This list, *Approved Drug Products with Therapeutic Equivalent Evaluations,* is commonly known as the "Orange Book." *See id.;* http://www.fda.gov/cder/ob/default.htm.

When filing an ANDA, the filer must also include, with the application, "the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug. . . ." 21 U.S.C. § 355(b)(1). An ANDA filer must certify, with respect to each patent that claims the listed drug, either that no patent was filed for the listed drug (a "paragraph I" certification), that the patent has expired (a "paragraph II" certification), that the patent will expire on a specified date and the ANDA filer will not market the drug until that date (a "paragraph III" certification), or that the

patent is invalid or would not be infringed by the manufacture, use, or sale of the new drug (a "paragraph IV" certification). 21 U.S.C. § 355(j)(2)(A)(vii).

An ANDA filer that elects a paragraph IV certification must notify each affected patent owner of the certification. *Id.* § 355(j)(2)(B)(I). The patent owner then has forty-five days after the date it receives such notice to bring suit against the ANDA filer for patent infringement. *Id.* § 355(j)(5)(B)(iii). If no patent owner brings such a lawsuit during this period, the FDA may immediately approve the ANDA. *Id.* If, however, the patent owner brings suit during this period, the FDA's final approval of the ANDA is stayed for thirty months after the date the patent owner received the requisite notice,[25] or until a district court returns a decision as to the validity of the patent or its infringement if it does so before the thirty-month period expires. *Id.*

ANDA applicants may also satisfy their obligation to address all relevant patents by filing a statement under 21 U.S.C. 355(j)(2)(viii) ("Section viii Statement"). By filing a Section viii Statement the applicant acknowledges that the drug sought to be manufactured is protected by a method of use patent, but claims that the applicant is not seeking approval for the patented use. An ANDA filer can submit either a Section viii Statement or a paragraph IV certification for each listed

25. The notices of paragraph IV certification that Takeda received from Mylan and Alphapharm are dated September 8, 2003, and January 29, 2004, respectively. Thus, the 30 month periods will run on March 8 and July 29, 2006.

patent, but not both. *See Purepac Pharm. Co. v. Thompson*, 354 F.3d 877, 880 (D.C.Cir.2004).

Any approval letter sent by the FDA before the expiration of the prescribed stay and before a court ruling of patent invalidity or non-infringement is tentative. *See* 21 C.F.R. § 314.105(d). If before the thirty months expire a court rules that the patent is either invalid or not infringed, the tentative approval of the ANDA is made effective as of the date of judgment. 21 U.S.C. § 355(j)(5)(B)(iii)(I). If after thirty months there has been no ruling on patent validity or infringement and the stay expires, the ANDA filer can distribute and market the drug but, depending on the court's later patent ruling, an ANDA filer that chooses to follow this course may thereafter become liable for damages if infringement is found. *In re Tamoxifen*, 429 F.3d at 376.

As an incentive for generic manufacturers to choose the paragraph IV certification route, and thereby to challenge weak patents, the Hatch-Waxman Act offers under certain conditions, the first ANDA filer with a paragraph IV certification the opportunity to market its generic drug exclusively for 180 days. To this end, the FDA may not approve the ANDA of a subsequent filer until 180 days after the earlier of the date 1) the first ANDA filer commercially markets the generic drug, or 2) a court of competent jurisdiction concludes that the

patent in question is invalid or not infringed. 21 U.S.C. § 355(j)(5)(B)(iv)(I)-(II).[26]

Alphapharm was the first to file an ANDA. Its submission to the FDA was ultimately rejected because it could not make a pill that was a bioequivalent to ACTOS®.[27] As a result, the second filer, Mylan, will enjoy the six month exclusivity period if the '777 Patent is invalidated.

U. The Defendants' ANDA Filings

On July 15, 2003, Watson Pharmaceuticals, Inc., Watson Laboratories, Inc., and Danbury Pharmacal, Inc. ("Watson"), Alphapharm, Ranbaxy Laboratories, Ltd., and Ranbaxy Pharmaceuticals, Inc. ("Ranbaxy"), and Mylan all filed ANDAs seeking approval to market 15 mg, 30 mg, and 45 mg pioglitazone hydrochloride tablets.

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26. Until 1998, the 180 day exclusivity period was available to the first ANDA filer to elect a paragraph IV certification only if it successfully defended a lawsuit for infringement of the relevant patent. *See* 21 C.F.R. § 314.107(c)(1) (1995). This "successful defense" rule was challenged and rejected by circuit courts in two separate lawsuits. *See, e.g., Mova Pharm. Corp. v. Shalala,* 140 F.3d 1060, 1076 (D.C.Cir.1998). The FDA formally revoked the "successful defense" requirement in 1998. *See* Effective Date of Approval of an Abbreviated New Drug Application, 63 Fed.Reg. 59,710, 59,710 (Nov. 5, 1998), 21 C.F.R. § 314.107 (1999).

27. It appears that the FDA rejected Alphapharm's ANDA at some point between its initial filing in July 2003, and its filing of a Section 355 Statement in January 2004.

Appendix B

Ranbaxy and Watson filed paragraph III certifications with respect to the '777 Patent; they did not challenge its validity, representing instead that they will not make, use, sell, or offer for sale their products until the expiration of the '777 Patent. Both Ranbaxy and Watson also filed paragraph IV certifications relating to the composition claims in the Combination Use Patents.[28]

Alphapharm filed a paragraph IV certification claiming that the '777 Patent is invalid. Alphapharm filed a Section viii Statement with the FDA with respect to the Combination Use Patents, asserting that it does not seek approval for any of the uses covered by those patents.

Mylan filed a paragraph IV certification with respect to the '777 Patent, claiming that it is invalid. With respect to the Combination Use Patents, Mylan filed a paragraph IV certification addressing the pharmaceutical composition claims of one of the patents and a Section viii Statement regarding the method claims.

V. The Alphapharm and Mylan Statements of Obviousness

In their paragraph IV certifications, both Alphapharm and Mylan claimed that the '777 Patent was invalid due to obviousness. Alphapharm and Mylan were required to send a notice of paragraph IV certification

28. Ranbaxy also included, with its Paragraph IV certification, Section viii Statements with respect to the method claims contained in the Combination Use Patents.

that included detailed statements of the legal basis of their positions that the '777 Patent was invalid ("Section 355 Statement"). *See* 21 U.S.C. § 355(j)(2)(b)(ii). By the time of trial, each defendant had radically altered the approach to the invalidity issue expressed in its statement. Mylan abandoned its articulated theory of obviousness in its entirety, and pursued an inequitable conduct claim at trial. Alphapharm altered its obviousness argument in several substantial ways. The following describes the parties' Section 355 Statements and compares them to the positions they took at trial.

Alphapharm's Section 355 Statement, dated January 29, 2004, recognized that it had the burden to prove by clear and convincing evidence that the prior art must provide some reason or motivation for a person of ordinary skill to make pioglitazone. It identified only two sources of prior art: the '200 Patent and Sohda II. As its position at trial evolved, it also argued that the divisional patents to the '200 Patent and a few articles in scientific journals were also prior art.

Insofar as the '200 Patent was concerned, Alphapharm argued in the Statement that the patent generically disclosed pioglitazone, and identified three compounds related to pioglitazone: compounds 16, 40, 42.[29] It noted that compound 42 is the methyl homolog of the ethyl compounds covered by Claim 1 of the '777

29. Compound 16 has an ethyl substituent on a phenyl ring. Compound 40 is the unsubstituted pyridyl ring known as compound 3894. Compound 42 has a 6-methyl substituent on a pyridyl ring; it is compound (b).

Patent, and argued that an exchange of an ethyl group for a methyl group would have been obvious.

Next, relying on the fact that two compounds discussed in Sohda II, compounds 11 and 14, are revealed in that article to have identical efficacy and yet differ only in that one has an ethyl substituent and another has a methyl substituent, Alphapharm contended that one of ordinary skill would conclude that the methyl and ethyl are "equivalent with respect to biological activity on a closely related analog of pioglitazone." In making this assertion, Alphapharm identified each compound as attached to a pyridyl ring. Neither compound has a pyridyl ring as its left end moiety and Alphapharm does not argue at trial that they do.[30]

At trial, Alphapharm concentrated on an entirely different compound described in Sohda II. It argued that the discussion in Sohda II of compound 58 (which had a higher combined efficacy score than either compound 11 or 14) would have led one of ordinary skill in the art to choose compound 58 as the lead compound for further development. That argument is not to be found in Alphapharm's Section 355 Statement.

Alphapharm also argued in its Section 355 Statement that both the '200 Patent and Sohda II identify ciglitazone as having low toxicity, and that Takeda did not demonstrate that pioglitazone was surprisingly superior to ciglitazone. Similarly, it contended that the

30. A benzene ring is at the left end of each compound.

'777 Patent alleges an entirely different activity for ciglitazone than was disclosed in Sohda II. Alphapharm did not pursue either theory concerning ciglitazone at trial.

Next, Alphapharm's Section 355 Statement argued that Table 1 in the '777 Patent does not support the superiority of pioglitazone, and that the testing methodology described in the patent is flawed. Specifically, Alphapharm argued that "many" of the toxicity values on Table 1 were not "statistically significant." Alphapharm did not make this argument at trial.

Alphapharm argued in its Section 355 Statement that the experiments underlying the testing of a compound's toxicity to the heart were "inherently flawed" since Table 1 in the '777 Patent indicated that pioglitazone did not cause heart enlargement with a dose of 100 mg/kg, while the prescribing information for ACTOS® advises that heart enlargement was observed at 4 mg/kg in rats. The screening tests that produced the Table 1 data were, as described in the Patent's Application, two-week tests. The tests to which the ACTOS® disclosure refers were long-term tests conducted by Upjohn in 1992. Alphapharm tried to use this flawed post-hoc reasoning at trial, and that effort was rejected.

In its Section 355 Statement, Alphapharm next argued that the examiner should not have found that Takeda presented sufficiently compelling evidence to overcome the prima facie obviousness of pioglitazone.

It pointed to the efficacy data for the rats, which showed that the ED^{25} values for all of the pyridyl ring compounds were comparable and that all have strong pharmacological activity. In a related argument, Alphapharm contended in its Section 355 Statement that Takeda did not present any data to the examiner to establish that the other three ethyl 2-pyridyl compounds covered by Claim 1 had surprising or unexpected results. At trial, the thrust of Alphapharm's evidence concerned compound (b), which Table 1 revealed was potent in both mice and rats, but highly toxic. Alphapharm did, however, particularly in its summation, try to fashion an argument about the ethyl compounds other than pioglitazone that are covered by the patent.

Mylan's Section 355 Statement, dated September 8, 2003, was far more straightforward. It also identified only two relevant pieces of prior art, the '200 Patent and Sohda II. It argued simply that one compound described in both, which had a benzene ring at the left end instead of a pyridyl ring, and which was identified in Sohda II as having high efficacy,[31] made the invention of pioglitazone obvious. According to Mylan, the two compounds are "bioisosteres," and their structural similarity made it obvious to replace a benzene ring with a pyridine ring.

Mylan incorrectly described the benzene compound both in terms of its structural relationship to pioglitazone

31. The benzene compound is compound 16 in the '200 Patent and compound 14 in Sohda II.

and in terms of its efficacy.[32] In any event, Mylan completely abandoned this theory of obviousness during the discovery period. It proceeded to trial on an inequitable conduct claim.

W. Procedural History

On September 16, 2003, Takeda sued Mylan, Watson and Ranbaxy. Takeda sued Alphapharm on March 12, 2004. Takeda alleged direct infringement of the claims of the '777 Patent against Mylan and Alphapharm, and sought a declaratory judgment of induced infringement of the claims of the Combination Use Patents against all four defendants. Takeda's action against Alphapharm was accepted as a related to the other three actions on March 18, 2004. In their answers, Mylan and Alphapharm both asserted that the '777 Patent was invalid on the ground of obviousness. Defendant Watson moved to dismiss as non-justiciable those claims in Takeda's complaint that alleged induced infringement of the Combination Use Patents. Watson's motion was denied because Takeda alleged "a controversy of sufficient immediacy." *Takeda Chem. Indus., Ltd. v. Watson Pharm., Inc.*, 329 F.Supp.2d 394, 403 (S.D.N.Y.2004). A July 20, 2004 Order set May 27, 2005 as the date by which fact discovery would end, and set January 16, 2006 as the trial date.[33]

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32. The compound had a combined efficacy score of 5; many compounds had higher scores.

33. The trial date was later moved to January 17, 2006, due to a federal holiday.

Appendix B

Alphapharm moved to dismiss nine of Takeda's claims relating to the Combination Use Patents on May 21, 2004. On the same day, Takeda moved to dismiss Alphapharm's affirmative defense and counterclaim for "patent misuse." Alphapharm's motion was denied by Order dated August 13, 2004. Takeda's motion to dismiss was granted in an Opinion that noted that Alphapharm had failed "to meet even the minimal requirements of notice pleading." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty. Ltd.*, 04 Civ.1966(DLC), 2004 WL 1872707 (S.D.N.Y. Aug. 19, 2004).

Mylan's substitution of an inequitable conduct claim for its obviousness theory occurred in 2005. By letter dated March 15, 2005, Mylan noted that it could not locate experiments in Takeda's laboratory notebooks to support all the data submitted to the PTO and raised for the first time an argument that Takeda may have procured the '777 Patent "through inequitable conduct." On April 25, in response to a contention interrogatory from Takeda, Mylan formally contended for the first time that the '777 Patent was unenforceable on the basis that Takeda had committed inequitable conduct in its prosecution of the '777 Patent.[34] On June 6, after the close of fact discovery, Mylan served supplemental responses to Takeda's interrogatories, in which it expressed the view that the '777 Patent was invalid on the basis of obviousness over

34. Despite this notice, in early June, Mylan's counsel refused to let the company's Rule 30(b)(6) witness explain the bases for Mylan's contention that the '777 Patent is invalid on grounds other than those disclosed in the Mylan's Section 355 Statement.

compound 57 from Sohda II,[35] a different compound from the one identified in Mylan's Section 355 Statement. Mylan's effort to substitute a new theory of obviousness was rejected in an Order of June 15. *Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 03 Civ. 8253(DLC), 2005 WL 1457696, at *2 (S.D.N.Y. June 15, 2005). *See also Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 03 Civ. 8253(DLC), 2005 WL 2092920, at *1 (S.D.N.Y. Aug. 31, 2005). Meanwhile, on June 15, Mylan was given leave to amend its answer to add a claim for inequitable conduct, essentially because of the "desire that issues, if at all possible, be addressed on the merits in litigation." *Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 03 Civ. 8253(DLC), 2006 WL 44053, at *1 n. 2 (S.D.N.Y. Jan. 9, 2006). Given its late notice of this new claim, Mylan was required to present all bases for the claim in its expert reports.

All four actions were consolidated for trial by Order dated October 13, 2005, although the '777 Patent issues were to be tried before the issues relating to the Combination Use Patents. By Order of December 30, 2005, the trial on the Combination Use Patents was severed.

Takeda, Alphapharm and Mylan moved *in limine* to strike testimony by or to preclude certain witnesses. Takeda moved against Mylan experts Hendry, Nusbaum, and Ronis. Alphapharm moved against Takeda experts Hendrickson, Inzucchi, Kettyle, Koller and Stoner.

35. Compound 57 is Takeda compound 3894, the unsubstituted 2-pyridyl.

Mylan moved against Stoner and to exclude a supplemental declaration from Landau. Mylan also moved to preclude Takeda from offering evidence of any missing laboratory notebooks.

Ronis' testimony was stricken to the extent it was not contained in his expert report. *Id.* at *2. Hendry's testimony was stricken to the extent it covered areas in which he had denied having expertise. *Id.* at *2-3. The motions addressed to testimony by Nusbaum and Stoner were granted to the extent they offered legal argument or opinions that went beyond their expertise. *Id.* at *3; *Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 03 Civ. 8253(DLC), 2006 WL 137374, at *2 (S.D.N.Y. Jan. 11, 2006). Landau's supplemental declaration was stricken. *Takeda*, 2006 WL 44053, at *3. Mylan's motion to exclude evidence of any missing notebooks was denied. *Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 03 Civ. 8253(DLC), 2006 WL 83112 (S.D.N.Y. Jan. 12, 2006).

Hendrickson's testimony was stricken to the extent he opined on the selection of lead compound. *Takeda*, 2006 WL 137374. The motions concerning Koller, *id.* at *2, and Inzucchi and Kettyle were denied, *Takeda Chem. Indus., Ltd. v. Mylan Labs., Inc.*, 03 Civ. 8253, 2006 WL 66480 (S.D.N.Y. Jan.12, 2006).

At trial Mylan offered into evidence the unredacted declarations from Hendry and Ronis that it had served with the Joint Pretrial Order. The unredacted Ronis declaration was submitted as an Offer of Proof pursuant to Rule 103 of the Federal Rules of Evidence. In making

its Offer of Proof, Mylan emphasized that it was not seeking to make a motion for reconsideration of the Court's decision to strike parts of Ronis' testimony, *Takeda*, 2006 WL 44053, and it is not being treated as such.[36]

Discussion

Alphapharm asserts that pioglitazone is obvious in light of the prior art. Mylan contends that Takeda engaged in inequitable conduct. For the following reasons, each of these arguments is rejected.

I. Obviousness

Inherent in the Constitution's grant of patent power to Congress is the requirement that a patent monopoly be conveyed only where there is "[i]nnovation, advancement, and things which add to the sum of useful knowledge." *Graham v. John Deere Co.*, 383 U.S. 1, 6, 86 S.Ct. 684, 15 L.Ed.2d 545 (1966). Through the 1952 Patent Act, Congress codified three conditions for patentability: novelty, utility, and non-obviousness. *Id.*

36. At trial, Takeda presented its evidence first. At the close of Takeda's case on January 25, both Takeda and Alphapharm moved for judgment as a matter of law under Rule 52(c). Fed.R.Civ.P. 52(c). Alphapharm had not carried its burden of showing obviousness at that point, and did not do so either through its later presentation of its own evidence. Since the burden rested on Alphapharm, it was not appropriate to grant Takeda's motion until Alphapharm had had an opportunity to present its case.

at 17, 86 S.Ct. 684; 35 U.S.C. § 101-103. It is the last of these three conditions on which Alphapharm rests its challenge to Takeda's '777 Patent.

A patent may not be obtained if "the differences between the subject matter sought to be patented and the prior art are such that *the subject matter as a whole would have been obvious* at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains." 35 U.S.C. § 103(a) (emphasis supplied). Section 103 emanates from the Supreme Court's nineteenth century decision in *Hotchkiss v. Greenwood*, 52 U.S.(11 How.) 248, 13 L.Ed. 683 (1850), and its progeny, which took a functional approach to patent analysis and eschewed labels. *Graham*, 383 U.S. at 12, 17, 86 S.Ct. 684. The talismanic statement of the obviousness inquiry appears in *Graham*, which identifies four factual underpinnings to a determination of obviousness: (1) the scope and content of the prior art, (2) the level of ordinary skill in the art, (3) the differences between the prior art and the claimed invention, and (4) objective indicia of non-obviousness. *Id.* at 17-18, 86 S.Ct. 684; *see Merck & Co., Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1372-73 (Fed.Cir.2005). The issue of obviousness is a question of law. *Richardson-Vicks Inc. v. Upjohn Co.*, 122 F.3d 1476, 1479 (Fed.Cir.1997).

The scope and content of the prior art includes art that is "reasonably pertinent to the particular problem with which the invention was involved." *Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 664 (Fed.Cir.2000) (citation

omitted). Prior art must be available before the date of invention. 35 U.S.C. § 103(a), *see Richardson-Vicks Inc.*, 122 F.3d at 1480. Prior art teaches away from an invention "when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of the applicant's invention." *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed.Cir.2005).

Whether the claimed invention is obvious must be evaluated from the perspective of a hypothetical person of ordinary skill in the art. *Ruiz*, 234 F.3d at 666. In determining what constitutes ordinary skill in the art, a court may consider "1) the types of problems encountered in the art; 2) the prior art solutions to those problems; 3) the rapidity with which innovations are made; 4) the sophistication of the technology; and 5) the educational level of active workers in the field." *Id.* at 666-67.

Secondary considerations or the objective indicia of non-obviousness include "commercial success, long-felt but unresolved need, failure of others, copying, and unexpected results." *Id.* at 662-63. These considerations are probative to the extent they "give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham*, 383 U.S. at 17-18, 86 S.Ct. 684. The "nexus" or causal relationship between the secondary consideration and the claimed invention should shed light on whether the invention was obvious or not. *See Merck*, 395 F.3d at 1376. A presumption that a patented invention is commercially successful arises when a patentee can demonstrate

"significant sales in a relevant market, and that the successful product is the invention disclosed and claimed in the patent." *Ecolochem, Inc. v. Southern California Edison Co.*, 227 F.3d 1361, 1377 (Fed.Cir.2000) (citation omitted).

Patents are presumed to be valid. 35 U.S.C. § 282. A party challenging a patent can establish a prima facie case of invalidity by showing that the invention is obvious under an analysis of the first three *Graham* factors. *Winner Intern. Royalty Corp. v. Wang*, 202 F.3d 1340, 1350 (Fed.Cir.2000). If a prima facie case of obviousness is established, the burden of production shifts to the party defending the patent to demonstrate non-obviousness under the fourth *Graham* factor. *Id.* The burden of persuasion, by clear and convincing evidence, always remains with the party asserting the invalidity of the patent. *Beckson Marine, Inc. v. NFM, Inc.*, 292 F.3d 718, 725 (Fed.Cir.2002). The burden is "especially difficult" if the challenger relies on prior art "that was before the patent examiner during prosecution." *Glaxo Group Ltd. v. Apotex, Inc.*, 376 F.3d 1339, 1348 (Fed.Cir.2004) (citation omitted). This added burden stems from the "deference that is due to a qualified government agency presumed to have properly done its job." *Ultra-Tex Surfaces, Inc. v. Hill Brothers Chem. Co.*, 204 F.3d 1360, 1367 (Fed.Cir.2000) (citation omitted).

A strand of the law of obviousness addresses patents protecting chemical compounds. In the case of a chemical compound, a prima facie case of obviousness exists where there is a "structural similarity between claimed and

prior art subject matter" and "the prior art gives reason or motivation to make the claimed compositions." *Yamanouchi Pharm. Co., Ltd. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339, 1343 (Fed.Cir.2000) (citation omitted). "[O]bviousness may render a claimed invention invalid where the record contains a suggestion or motivation to modify the prior art teaching to obtain the claimed invention." *Beckson*, 292 F.3d at 727. Thus, an invention is prima facie obvious where the prior art would imbue one of ordinary skill in the art with a "reasonable expectation of success" in achieving the goals that the inventor sought to accomplish by transforming a compound in the prior art into the structurally similar claimed invention. *Yamanouchi*, 231 F.3d at 1343 (citation omitted). While a reasonable expectation of success must be shown, in order to show prima facie obviousness it is not necessary to show that success was absolutely predictable. *Id.*

Where the creation of a chemical compound requires the chemist to pursue several steps in manipulating a compound revealed in the prior art, the patent challenger must show that one of ordinary skill in the art would have had sufficient motivation to take each of those steps. *Id.* at 1344-45. Similarly, if the prior art "offers no suggestion to pursue the particular order" of manipulations that led to an invention, and where a deviation in the order would have taught away from the invention, then the challenger must show what would have led any ordinary artisan in the field "to follow the precise steps that produced a remarkable invention." *Id.* at 1345.

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A prima facie case of obviousness may be rebutted by "showing that the claimed compositions possess unexpectedly improved properties or properties that the prior art does not have." *Dillon*, 919 F.2d at 692-93. When rebuttal evidence is submitted, "all the evidence must be considered anew." *In re Eli Lilly and Co.*, 902 F.2d 943, 945 (Fed.Cir.1990); *see also Glaxo Group Ltd.*, 376 F.3d at 1349; *Richardson-Vicks*, 122 F.3d at 1482-83.

Alphapharm contends that pioglitazone is prima facie obvious over the prior art compound (b) from Table 1 of the '777 Patent, which had been identified in both the '200 Patent and Sohda II. Alphapharm argues that the prior art clearly identified compound (b) as a lead compound warranting further investigation, and that the application of a few, obvious chemical processes would have produced pioglitazone. Turning to objective evidence of pioglitazone's obviousness, Alphapharm contends that pioglitazone's lack of toxicity is not unexpected because variability among compounds is "inherent". As for its commercial success, Alphapharm argues that the success of ACTOS® must be discounted because *inter alia* pioglitazone was not the first TZD on the market and is not the only successful TZD still on the market. These and Alphapharm's other arguments are described in detail below.[37]

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37. It has been challenging to capture Alphapharm's arguments because it has presented a constantly shifting set of arguments, abandoning some, inventing others, and even contradicting itself as the trial progressed. Nonetheless, every effort has been made to address each of the principal arguments raised during the trial by Alphapharm.

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Alphapharm's arguments fall woefully short of the mark. The prior art did not disclose or suggest either the pioglitazone molecule itself or how to make it. Alphapharm has not shown by any persuasive evidence, much less by clear and convincing evidence, that one with ordinary skill in the art would have had any reasonable expectation based on the prior art that synthesizing pioglitazone would result in the discovery of a non-toxic, effective treatment for diabetes, and therefore would not have had any motivation to do so. To begin with, the evidence is overwhelming that one skilled in the art would not have, based on the prior art, chosen compound (b) as a lead compound. Beyond that, Alphapharm has not shown that the ordinary artisan would have had sufficient motivation to take each of the several conceptual and experimental steps that were necessary to move beyond compound (b) and create the pioglitazone molecule.

Even if Alphapharm had been able to show a prima facie case of obviousness, there is compelling and conclusive evidence that pioglitazone's non-toxicity was unexpected. Alphapharm is unable to overcome the extreme differences in the toxicity profiles between pioglitazone and prior art compound (b), whose modification it contends would have led to the discovery of pioglitazone. Confronted with overwhelming evidence that the non-toxicity of pioglitazone was entirely unexpected given the high toxicity of compound (b), including the admission of Alphapharm's own expert that there was no reasonable basis to expect that pioglitazone would be non-toxic, Alphapharm ignores the relevant

legal standard and argues simply that there is so much variability in the pharmacological effects of compounds, even compounds that share similar structures, that a compound's non-toxicity is "not surprising." This does not carry Alphapharm's burden of showing obviousness. The discussion that follows examines each of the Graham factors, paying particular attention to the identification of a lead compound, the motivation to alter that compound, and unexpected results.

A. Qualifications of a Person of Ordinary Skill in the Art

The parties agree that a person with ordinary skill in the art would have a graduate degree in chemistry or a relevant branch of chemistry and practical experience applying that education by working at or consulting with a pharmaceutical company in the development of pharmaceutical compounds.[38] It is unnecessary to refine further the minimum qualifications of a person with ordinary skill in the art, since nothing that follows in this analysis turns on the presence of a more precisely drawn definition.

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38. Alphapharm defines someone of ordinary skill in the art as a person who would have secured a Ph.D. in medicinal chemistry or a related field, done postdoctoral work for two to three years and thereafter worked for a pharmaceutical company for two to three years. Takeda defines the person as someone with a Master's Degree in chemistry or chemical engineering with four years experience in the research and development of pharmaceuticals or medical organic compounds, or someone with a Ph.D. in chemistry or chemical engineering with two years of experience in the research and development of pharmaceuticals or medicinal organic compounds.

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Alphapharm has argued that one of Takeda's experts, Danishefsky, is not qualified to opine about what one with ordinary skill in the art of medicinal chemistry would understand or do since he is a synthetic organic chemist. Danishefsky is a renowned synthetic organic chemist who has devoted his entire career to exploring the issues of medicinal chemistry.[39] He supervises the training of medicinal chemists, has recently been nominated to receive a lifetime achievement award in chemistry from a major pharmaceutical company,[40] and regularly consults with major hospitals and pharmaceutical companies on issues of medicinal chemistry. He is superbly qualified to opine in the field of medicinal chemistry.

B. Relevant Prior Art

As noted above, Takeda applied in Japan for what became known as the '777 Patent in January 1985, and in the United States in January 1986; the '777 Patent issued on August 18, 1987. It is undisputed that the relevant prior art for the '777 Patent includes the '200 Patent, issued in 1981; and Sohda II, published in 1982,

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39. Takeda brought to this trial experts of extraordinary accomplishment and distinction. Many of them, including Danishefsky, were preeminent in their field of endeavor. These were scientists whose knowledge and opinions were uniformly helpful to the Court in understanding the science at issue here.

40. Danishefsky will receive a lifetime achievement award from Bristol-Myers Squibb in May 2006 and the National Academy of Science's medal in chemical sciences in April 2006.

both of which were identified by Takeda in its application for the '777 Patent. The '200 Patent first disclosed the compound on which Alphapharm relies for its obviousness argument, compound (b).[41] Alphapharm's expert identifies Sohda II as the "key" piece of prior art on which the skilled artisan would have relied to identify compound (b) as the lead compound for further investigation.[42]

Although Alphapharm's Rule 30(b)(6) witness testified that Alphapharm was not aware of any prior art that Takeda failed to put before the examiner, at trial Alphapharm identified two additional patents and one other article as prior art. It asserts that two divisional patents for the '200 Patent, the '605 and '779 Patents, issued on July 20, 1982, and April 24, 1984, respectively, and their prosecution histories, should also be considered relevant prior art.[43] In particular, it asserts that the prosecution history of the '779 Patent, which was available to the public through examination in Washington, D.C. when the '779 patent was issued, would

41. Compound (b) from Table 1 is a 6-methyl, which was identified in the '200 Patent as compound 42.

42. While Alphapharm began the trial by identifying Sohda II as the critical writing which would have led one skilled in the art to identify compound (b) as a lead compound, in the face of overwhelming evidence to the contrary, by the end of the trial it had virtually abandoned reliance on Sohda II.

43. Takeda disputes that these patents can properly be considered prior art.

have assisted those with ordinary skill in the art in selecting compound (b) as a lead compound for further investigation. Finally, Alphapharm identifies an article in a peer reviewed scientific journal: Nohara, A. et al., "Studies of Antianaphylactic Agents. 6.1 Synthesis of Some Metabolites of 6-Ethyl-3(1H-tetrazol-5-yl) chromone and their Analogues," *Journal of Medicinal Chemistry,* 22:3, 290-295 (1979) ("Nohara Article").[44] Mosberg gleaned from the Nohara Article that persons of ordinary skill in the art, including Takeda, practiced the synthesis of routine homologs to improve promising drug compounds as of 1979.

C. Differences Between the Prior Art and Pioglitazone

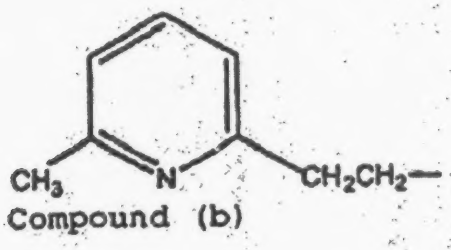
Alphapharm's assertion of obviousness rests on two claims: that it would have been obvious to select a single compound from the prior art-a 6-methyl on a pyridyl ring, which is compound (b) on Table 1 of the '777 Patent-as the "lead compound" for development, and that it would have been obvious to create and test the compounds that lie between the 6-methyl and pioglitazone, which is a 5-ethyl on a pyridyl ring.[45] The

44. Alphapharm has abandoned its contention that a second article, Cunningham, S. et al., "The Characterization and Energetic Potential of Brown Adipose Tissue on Man", *Clinical Science* 69, 343-348 (1985) ("Cunningham Article"), was prior art. Alphapharm's expert used the Cunningham Article to educate himself about how persons of ordinary skill viewed the issue of brown fat in the 1980's. Compound (b) was identified in Sohda II as increasing brown fat.

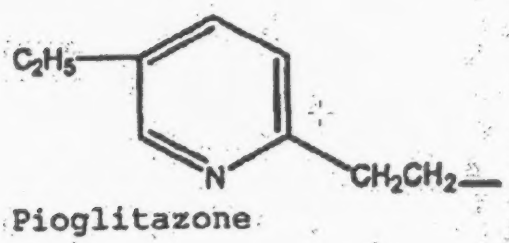
45. As already noted, a methyl group contains one carbon, while an ethyl group contains two carbons.

program would have entailed synthesizing compounds in which a methyl appears at each of the open positions on the pyridyl ring, a process that Alphapharm terms "walking the ring", and also synthesizing compounds in which the substituent on the pyridyl ring at each of these positions is an ethyl instead of a methyl, a process referred to as "homologation".

The following diagrams of the left end of compound (b) and pioglitazone illustrate the changes in the molecular structure that were necessary to make the transformation.



Compound (b)



Pioglitazone

Both of these structures are on a pyridyl ring.[46] Compound (b) has a substituent added at the 6th position on the ring; pioglitazone's substituent is added at the 5th position, counting counter-clockwise from the nitrogen atom on the ring.

1) Identification of a Lead Compound

Alphapharm's obviousness argument relies in the first instance on its contention that one skilled in the art would have recognized compound (b) as the lead compound for further development.[47] Alphapharm's expert has rested his identification of compound (b) as a lead compound on his reading of the '200 Patent and Sohda II.

As described above, the '200 Patent provided protection for TZD derivatives. The molecular structure of compound (b) was illustrated in the patent as one of fifty-four examples of TZD compounds with a certain structure that had been synthesized through steps

46. For ease of reference, certain explanations are repeated here. Pyridyl denotes a six-membered ring of five carbon atoms and one nitrogen atom. The numbering on a ring begins with the highest atomic weight atom in the ring, which in this case is nitrogen. The numbering moves in a counterclockwise fashion.

47. Alphapharm's Section 355 Statement did not explain why compound (b) would be chosen as a lead compound over others described in either the '200 Patent or Sohda II. Alphapharm has abandoned its assertion in its Section 355 Statement that pioglitazone was obvious based on an analysis of compounds 11 and 14 in Sohda II.

described in the patent. Examples of still more TZD compounds synthesized through other procedures were also illustrated. The prosecution history of the '200 Patent includes some test results for nine compounds that were presented to the PTO as "typical" of compounds covered by the disclosed invention in order to demonstrate that TZD compounds covered by the invention were "far superior" in their blood glucose and plasma triglyceride lowering effects than compounds in the prior art. Compound (b) was one of the nine whose test results were charted, and it was one of three such compounds charted in the '200 Patent that had the best disclosed performance.[48]

Since Takeda only presented test results for nine of the hundreds of millions of TZD compounds covered by the patent application, one with ordinary skill in the art would have had no reasonable basis to conclude that these nine were the best performing of all of the compounds tested by Takeda, and thus that one of these nine should be selected as the lead compound for further development. Even if one could make that leap, however, the prosecution history for the '200 Patent disclosed two other compounds, in addition to compound (b), that appeared to have superior performance among the nine that were tested. And, the next year, when Sohda II was published, compound (b) was not singled out as one of the best performing compounds.

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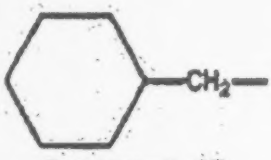
48. Of the nine, three compounds, including compound (b), had a combined score of 7; five had a score of 6; one had a score of 2.

Appendix B

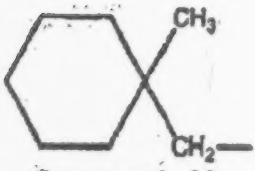
Sohda II, which has also been described above, reported test results on 101 TZD compounds, and identified three that "exhibited the most favorable properties in terms of activity and toxicity." Each of these three compounds had a different left moiety, and therefore, provided different starting points from which one of ordinary skill in the art could make changes in the hope of identifying successful compounds. Compound 47 terminated with an unsubstituted cyclohexane ring[49] and is connected to the rest of the compound by a CH^2. Compound 49, which is ciglitazone, has a similar structure to compound 47, however, there is methyl substituent at the point of attachment to the rest of the compound. Compound 59 is the only one of the three with a pyridyl ring at the left end moiety, however, it is a 3-pyridyl ring. (Pioglitazone's pyridyl ring is a 2-pyridyl

49. A cyclohexane ring is a saturated ring of six carbons.

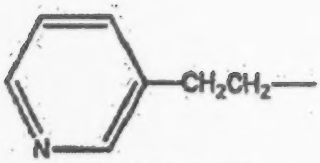
ring.[50]) The following diagrams illustrate the differences in the left end of these structures more effectively than a narrative description.



Compound 47



Compound 49



Compound 59

Compound (b) was among the 101 whose test results were reported in Sohda II, but it was *not* one of the three

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50. The 2-pyridyl is attached to the remainder of the TZD molecule at the second position on the pyridyl ring; the 3-pyridyl, at the third position.

compounds identified by the authors as having the most favorable performance.

Sohda II gave detailed efficacy data, but did not set out the toxicity test results in comparable chart form. It did discuss in its narrative sections, however, various toxicity and side effect issues which eliminated some of the compounds with strong efficacy ratings from being singled out for their overall performance. For example, seven compounds had the highest combined efficacy score, which was a rating of 7. Sohda II identified problems with toxicity or side effects for six of the seven compounds.[51] Compound (b) was one of the seven, but was described as causing "considerable increases in body weight and brown fat weight."[52] The three compounds that were identified as having the most favorable performance each had a combined efficacy score of only 5.[53]

A person with ordinary skill in the art would had concluded from an examination of the '200 Patent,

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51. The one compound that scored 7 and yet had no identified problems was compound 99. Its structure at the left end moiety differs significantly from the pyridyl.

52. Compound 3894, which had a combined potency score of five, was described as having the same problematic side effects as compound (b).

53. Of the 101 compounds in Sohda II, 39 had a combined score of 5 or higher. Twenty-nine of the thirty-nine had been described in the '200 Patent.

including its file wrapper, and of Sohda II, that the three compounds identified in Sohda II as promising should be the starting point for further investigation. There were literally thousands of different substituents that one of ordinary skill in the art could consider in modifying those three compounds. Such a person would certainly not have concluded that compound (b) should be chosen as a lead compound over the many other more obvious or at the very least similarly interesting choices presented by that prior art. Indeed, Sohda II teaches away from compound (b) when it specifically comments on its negative effects on body weight and brown fat. Type 2 diabetes is a chronic disease. Any effective drug will be given over a long period of time, and therefore, those of ordinary skill in the art would have been especially sensitive to toxicity and side-effects.

History confirms this analysis. Takeda and another pharmaceutical company worked extensively to develop one of the three compounds identified by Sohda II as particularly promising, before abandoning it because of its toxicity. Ciglitazone was Sohda II's compound 49, and was withdrawn by Takeda from further development during human testing both because it failed the chick lens assay test and due to efficacy concerns.

In fact, because of concerns over toxicity in treating a chronic disease like diabetes, one skilled in the art would have been more likely to choose as a starting point for further research one of the many compounds in Sohda II, and there were over ninety, where the authors did not disclose the existence of toxicity or side effects, and

to engage in research to increase the efficacy and confirm the absence of toxicity of those compounds, than to choose as a starting point a compound with identified adverse effects. If for some yet unexplained reason one chose to start with a compound that had identified problems, one skilled in the art would be motivated to make fairly radical changes to it in order to try to overcome the problems.

Admissions from an Alphapharm scientist confirm that there was no basis to select compound (b) (that is compound 58 from Sohda II) as a lead compound other than hindsight. At his deposition, Rosenberg, who is the head of Alphapharm's intellectual property department and who was also the scientist who formulated its Section 355 Statement, admitted that there was "nothing to recommend" compound (b) over any of the other compounds that had a combined score of 7, and that he only chose compound (b) from Sohda II "because it was similar to pioglitazone."

During his cross-examination, Alphapharm's expert Mosberg presented a new and remarkable explanation for why compound (b) would have been selected as the lead compound by one of ordinary skill in the art over the other six compounds with a rating of 7 and over the three compounds singled out for favorable mention in Sohda II. He argued that it appeared from Sohda II that each of these other compounds, and the molecules closely related to them, were being pursued actively by Takeda and that it would be impractical to compete with Takeda, given its head start, and to invest precious research

resources into the compounds Takeda was investigating. This argument was not presented by Mosberg in his direct testimony, where he essentially ignored the existence of the other compounds that scored 7 and the three compounds given prominence in Sohda II. It also directly contradicts his direct testimony, where he asserted that compound (b) would have been selected as a lead compound by one skilled in the art because of the evidence that Takeda was "zeroing in on substituted pyridyl rings."[54]

In any event, there are a myriad of problems with Mosberg's recently invented analysis. First, it is not supported by any intellectually rigorous analysis. Second, the test is not whether a compound seems an unpopular candidate for development among competitors but rather whether one of ordinary skill in the art would have been motivated to choose it as a lead compound in an effort to develop a safe and effective drug to treat diabetes. Third, Mosberg's analysis completely undercuts Alphapharm's contention that compound (b) was the obvious lead compound for investigation. Surely, under Mosberg's revisionist reading of Sohda II, the compounds in which Takeda seemed to be expressing an interest were the more appropriate choices for one skilled in the art who was seeking to find a successful

54. Mosberg's trial testimony also directly contradicts Alphapharm's proposed findings of fact submitted before trial, which indicate that it hoped to establish that one skilled in the art would have understood that Takeda was focusing its attention on compound (b).

anti-diabetic agent, instead of compound (b), which he believes Takeda had abandoned.

Mosberg also tries to transform its identified problems of an increase in body weight and brown fat into an advantage for compound (b). He argues, with some creativity but little persuasion, that these identified problems would only "motivate one of skill in the art to make changes" in the compound.[55] Such a response does not explain, however, why compound (b), with its associated problems, should be chosen as the lead compound for further investigation.

Mosberg makes two other arguments in an effort to explain why compound (b) would be selected as a lead compound. First, Mosberg argues that further support for focusing on compound (b) comes from the '779 Patent, which specifically claims over sixty compounds including compound (b). Alphapharm's Section 355 Statement did not identify the '779 Patent as relevant prior art.

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55. It is undisputed that weight management is an important element in the treatment of Type 2 diabetes and that this was understood in the 1980s. Takeda's expert opines persuasively that the Cunningham Article, which warned that "considerable caution" should used in extrapolating animal studies' brown fat findings to humans, would not have diminished the negative impact of the statements about weight gain in Sohda II on a scientist evaluating compound (b) for exploration. Mylan's Rule 30(b)(6) witness opined that one of ordinary skill in the art would rule out compound (b) as a compound of interest because of its negative profile disclosed in Sohda II.

Appendix B

As already described, it was the PTO's initial rejection of the '200 Patent that led Takeda subsequently to file the '605, '779, and '141 divisional patents. Because they are divisional patents, the text of each of the divisional patents is identical to the text of the '200 Patent. The '200 Patent discloses hundreds of millions of TZD compounds. The divisional patents are directed to subsets of those compounds covered by the generic disclosure in the '200 Patent. The '779 Patent, which was filed after the '605 Patent, actually claims a larger class of compounds than the '605 Patent. The '605 Patent claims 1080 compounds, while the '779 Patent claims over one million compounds.[56] These patents claimed not only pyridyl derivatives but also thiazolyl derivatives.

Takeda filed the application for what became the '779 Patent on March 15, 1983, identifying through supporting diagrams over 60 compounds that were TZD derivatives. Essentially, the claims were directed to a structure with a pyridyl or a thiazolyl group at the left end of the TZD molecule, with one to three substituents on those rings, the substituents being selected from lower alkyls, halogens and hydroxyl. Two compounds were specifically claimed, compound (b) and a thiazolyl.[57] Compound (b) was also diagramed as compound 42 on the application. In a preliminary amendment of the same date, Takeda stated, "the compounds in which these

56. These numbers do not include the salts and stereoisomers covered by the patents.

57. The thiazolyl was a 4-methyl 5-thiazolyl.

heterocyclic rings are substituted have become important, especially Compound 42."

There are several problems with Alphapharm's reliance on the '779 Patent.[58] Takeda's expert has given compelling evidence that medicinal chemists do not consider arguments made by patent counsel, particularly when there is contrary information in peer-reviewed literature (such as Sohda II), and that he has never known anyone in his over forty years of work in the field of medicinal chemistry to establish research priorities in this way. Alphapharm's expert essentially agreed, and Alphapharm has presented no evidence to the contrary.[59]

Moreover, if Alphapharm wishes now to rely on a divisional patent as prior art to explain why one skilled in the art would select compound (b) as a lead compound, then it is necessary to consider what one skilled in the art would have concluded by an examination of each of the Takeda TZD patents that had issued by this time.

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58. Alphapharm may also be attempting to make an inequitable conduct argument concerning the presentation of the toxicity data for compound (b) in the '777 Patent by comparing it to general statements in the '779 Patent about toxicity levels in TZD derivatives. The comparison is spurious and does not require further discussion.

59. In addition, the file wrapper for the '779 Patent was simply not accessible to one of ordinary skill in the art. As of 1983, patent applications were not prosecuted publicly and the application would not have been available to the public until the patent had issued on April 24, 1984. At that time, the file history would have had to be specially obtained at the patent office.

Taken together, they show that Takeda was actively conducting research in many directions, and had not narrowed its focus to compound (b).

Finally, in support of Alphapharm's argument that compound (b) would have been selected as the lead compound from the prior art, in particular from Sohda II, Mosberg contends that one of ordinary skill in the art would have observed that the four compounds revealed in Sohda II with a pyridyl ring on the left hand side of the structure, display high potency and that of those compounds the compound with the methyl substituent, that is compound (b) or 58, had the highest potency. He points with emphasis to the fact that the substituted pyridyl has a higher combined efficacy score than the unsubstituted pyridyl.[60] From that, Mosberg suggests that one of ordinary skill in the art would have concluded that the methyl substituent was responsible for increasing potency and thus would have been strongly motivated to attempt further substituent replacement to reduce the unwanted side effects of the 6-methyl, while maintaining its potency.

This argument benefits entirely from hindsight. Sohda II describes several clusters of efficacious compounds, including the cluster into which compounds 47 and 49 fall, compounds 47 and 49 being two of the three compounds given particular attention by the authors. In any event, of the cluster into which compound

60. The unsubstituted 2-pyridyl (compound 57) had a combined score of 5, while the 2-pyridyl with a methyl at the 6 position (compound 58) had a combined score of 7.

(b) falls, the most obvious candidate for a lead compound is the one identified by the article for further investigation, that is compound 59, since the article reported no toxicity or harmful side effects for that compound. Exploration of that compound, which has a 3-pyridyl ring at its left end rather than the 2-pyridyl ring shared by pioglitazone and compound (b), would of course have led in a different direction.[61]

In sum, Alphapharm has failed to show that compound (b) would have been understood by one skilled in the art as a lead compound. There is no support for such a finding based on the prior art that Alphapharm identified in its Section 355 Statement: the '200 Patent and Sohda II. Thus, it now turns to a statement about compound (b) in application for the '779 Patent. One skilled in the art would not have relied on that reference to identify compound (b) as a lead compound given the more exhaustive and reliable scientific analysis presented by Sohda II, which taught away from compound (b), and the evidence from all of the TZD patents that Takeda filed contemporaneously with the '779 Patent showing that there were many promising, broad avenues for further research.

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61. At his deposition Mosberg admitted that one skilled in the art would have been led to investigate all of the compounds based on the 2-, 3-, and 4-pyridyl ring, with less emphasis on the 4-pyridyl compounds.

2) Motivation to Create Pioglitazone

Assuming that compound (b) would have been identified by one skilled in the art as a lead compound, Alphapharm has not shown that such a person would have been motivated to synthesize the compounds that had to be created to find pioglitazone. First, one skilled in the art would have done an initial screening of compound (b) for toxicity and concluded that its toxicity made it an extremely poor candidate for modification.[62] The likely course of action at that point, would have been to return to the compounds actually identified in Sohda II as worthy of further research.[63] Second, Alphapharm has failed to point to anything in the prior art that would have presented one skilled in the art with a reasonable expectation of success in creating the compound that became pioglitazone.

Before addressing Alphapharm's specific arguments, it is useful to describe briefly some of the

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62. As indicated on Table 1 to the '777 Patent, compound (b) was extremely toxic to the liver, heart, and blood.

63. There is no contention that the investigation of the three compounds identified in Sohda II as worthy of further investigation would have led with sufficient directness to pioglitazone. As already noted, among other things, two did not have a pyridyl ring on the left moiety, and the left moiety in the third was a 3-pyridyl ring rather than the 2-pyridyl ring in the pioglitazone molecule, meaning that its attachment to the remainder of the TZD molecule was from a different point on the pyridine ring.

pertinent chemistry and research issues that one skilled in the art would have faced in the 1980s. Many of the tools that assist today in the process of chemical synthesis were not available in the 1980s. At that time, the process of discovering new compounds for pharmaceutical development involved the screening of sample collections, usually those already in the libraries of the pharmaceutical company, or those created by the chemistry laboratories of the company. When a lead compound was identified, a lead compound being one that contains suggestive properties that are indicative of possibilities for progress, the scientist would modify the lead compound to achieve the right balance of potency and non-toxicity. The modification process was not routine. The chemistry laboratories of the company needed to create, through chemical synthesis, each new compound that needed its potency and toxicity tested. The conceptual acts of moving a methyl substituent to another position on a ring and of replacing it with an ethyl substituent require different starting materials and different chemical processes. While it may be easy to describe in English, the science is time-consuming.

The left-hand end of the TZD molecule is known as a terminating region, and is a so-called hot spot, where small changes can have dramatic repercussions in performance. It would have been a significant research project to understand the consequences of even small modifications to this region of the molecule, and one skilled in the art would not have had any reasonable basis to expect that even small changes in this area would result in an increase as opposed to a decrease in either

the efficacy or toxicity of the molecule in any particular organ or body system much less in the body as a whole. There was absolutely no basis whatsoever to form a belief that any particular modification would change a toxic molecule into a non-toxic compound. There was simply no scientific literature which explained how the particular changes to a molecule that are at issue here would lead to a drug with particular effects, whether for better or worse, in the body. As of the 1980s, and even today, the actual mechanism through which a TZD molecule interacts with the body's processes is not understood. In the 1980s, for instance, scientists did not know the shape of the insulin receptor or the specific molecular target for the TZD compound.

Predicting toxicity based on the structure of a compound is particularly difficult. And, in selecting a lead compound for development of a drug to treat a chronic disease, one skilled in the art would have been particularly sensitive to issues of toxicity. As a result of all of these challenges, it is not uncommon to synthesize thousands of compounds before arriving at a new drug that survives all review and enters the pharmaceutical market in the United States. Alphapharm's expert estimates that, even when one has identified a lead compound, success is achieved in at most 1% of research projects.

Alphapharm's expert, Mosberg, argues that the twin steps of "walking the methyl around the ring" and "homologation" to create an ethyl from a methyl are routine steps in the drug optimization process that would

have been performed by one of ordinary skill in the art and would have led quite directly to the discovery of pioglitazone from the investigation of compound (b). Mosberg's opinion was completely undermined by the other evidence presented at trial, including the far more credible testimony from Takeda's experts. It was also contradicted by Alphapharm's in-house medicinal chemist whose deposition testimony was partially adopted as Rule 30(b)(6) testimony for Alphapharm.[64] Rosenberg testified that in making changes to the pyridyl ring on the left end of the TZD molecule, one would look at a host of substituents, such as chlorides, halides and others, not just methyls. He did not even mention ethyls.

a) Walking the Ring

Nothing in the prior art teaches that changing the position of the methyl substituent on the pyridyl ring could be expected to have a beneficial effect. Indeed, the prior art teaches that the results of a modification like walking a substituent around a ring were highly unpredictable.

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64. Alphapharm had identified Rosenberg as one of its trial experts, and had served his expert report. After he was deposed, however, Alphapharm withdrew its offer of Rosenberg as an expert at trial. Before making that decision, Alphapharm had adopted portions of Rosenberg's deposition testimony as evidence given by Alphapharm pursuant to Rule 30(b)(6), Fed.R.Civ.P.

Appendix B

Sohda II has only one pyridyl with a methyl substituent, compound 58. There is nothing in Sohda II from which one skilled in the art would conclude that a methyl in a different position on the pyridyl ring would improve efficacy or avoid or reduce compound 58's identified negative side effects.

Mosberg opines that the '200 Patent teaches that walking a substituent around the ring was a process "known" to Takeda. Many common (as well as sophisticated) chemical processes were no doubt known to Takeda; that is beside the point. The issue is whether there was any ground for a reasonable expectation of success that can be located in the prior art by a person of ordinary skill to choose a particular process to achieve the desired goal.

Mosberg gives three sets of examples[65] from the illustrations in the '200 Patent that show either a methoxy (CH_3O) or a chloro (Cl) being "walked around" a different ring, a benzene ring.[66] He does not assert, however, that any of the disclosed results from that process taught that such a process would be likely to lead to any success, or that any particular position on a

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65. Mosberg discusses compounds 1 and 2; compounds 18 and 19; and compounds 31, 32 and 33 from the '200 Patent. In Sohda II, these are compounds 32 and 31; compounds 13 and 12; and compounds 5, 4, and 3, respectively.

66. A benzene ring, in contrast to a pyridyl ring, does not have a nitrogen atom. A compound with a benzene ring is referred to as a pheryl.

ring was likely to more efficacious or less toxic than any other. None of the three examples includes a substituent at the 5th position on the ring, where pioglitazone's substituent is located.

An examination of the efficacy data from Sohda II for the phenyl compounds to which Mosberg points suggests that substituents in a lower ring position may be more potent, principally by comparing the efficacy scores for substituents in the 4th position with those in the 2nd position.[67] Alphapharm has not shown, however, that one skilled in the art would have understood that these results were transferable from a phenyl to a pyridyl compound, that they would pertain to a comparison between a substituent in the 6th and 5th positions, or that they would eliminate toxicity.

Mosberg argues that Takeda's historical experience confirms his opinion that it was expected that one would simply walk the methyl around the ring. This is, of course, an improper use of hindsight. Nonetheless, Takeda's historical experience is directly to the contrary. Compounds (c), (d) and (e) were each first synthesized in 1983; pioglitazone was first synthesized in 1982. Takeda clearly did not move from compound (b), which had been synthesized in 1978, to pioglitazone by "walking the ring."

Even if Takeda had moved away from compound (b) by "walking the ring," it would have discovered

67. Alphapharm did not make this comparison or argument at trial.

significant toxicity problems as soon as it synthesized and then tested each of the other methyl substituents on the 2-pyridyl ring. As illustrated in Table 1, compounds (d) and (e) each have significant toxicity. Compound (c) failed the chick lens assay screening. In sum, Alphapharm has not shown that one skilled in the art would have been motivated to move to pioglitazone by "walking the ring."

b) Homologation

Alphapharm has no more success with its argument that one skilled in the art would have been led to create a homolog of a methyl substituent on the 2-pyridyl ring,[68] than it did with its ring-walking argument. Alphapharm has failed to show that the prior art would have invested in a person with ordinary skill in the art a reasonable expectation that the substitution of an ethyl for an methyl would lead to beneficial results.

Sohda II describes over a score of compounds with a methyl substituent and eight compounds with an ethyl substituent. There is no discernable pattern of biological activity associated in a comparison of the two substituents in the prior art. Nothing in the prior art suggests that the process of substituting an ethyl for a methyl would be of any more assistance than using any other of the many possible substituents or changing

68. As noted earlier in this Opinion, a homolog is a chemical structure that differs from the parent compound by a single, constant increment of one carbon (and associated hydrogen atoms), such as adding a methyl group.

course entirely and adopting a base structure other than the 2-pyridyl ring.

Indeed, Alphapharm has not identified any basis to find that even those with great skill understood in the 1980's (or even today) that the substitution of an ethyl group for a methyl group is likely to have a beneficial effect on biological processes. Our understanding of the biological properties of compounds is too rudimentary even today to allow us to form reasonable expectations regarding such a result.

In particular, Alphapharm is confronted again with the significant hurdle placed by the toxicity found in compound (b). Having found such high levels of toxicity to the heart, liver, and blood cells in compound (b), it has not pointed to anything in the prior art that would suggest that creating a homolog of the compound would be likely to reduce much less eliminate toxicity, either in any particular body system or as a whole.[69]

Ignoring entirely the substantial issue of compound (b)'s toxicity, Mosberg asserts that Sohda II teaches that the substitution of a methyl increases potency, and specifically that a comparison of Compounds 57 and 58

69. If one of ordinary skill in the art were confronted with toxicity issues, she would be "well-advised," according to Danishefsky, to try substituents that would change significantly the dipole moment of the molecule, that is the electron density of the compound. Examples of such substituents do not include an ethyl, and do include methoxies, alcohols, and halides, among many others.

in Sohda II demonstrates that homologation increased the efficacy of pyridine compounds. Compound 57 is the unsubstituted pyridine ring; compound 58 is compound (b) (the 6-methyl on the pyridine ring).[70]

A more straightforward reading of Sohda II indicates that its authors understood that homologation does not ameliorate toxicity. The Sohda II authors point out that "[a]lthough compounds 56, 57, 58, 59 and 63 in Table IV showed potent activities, they, *especially 57 and 58,* caused considerable increases in body weight and brown fat weight." (Emphasis added.) One of ordinary skill in the art would therefore have been more likely to conclude from Sohda II that homologation had no tendency to decrease unwanted side effects and to focus research efforts elsewhere. There were other compounds described in Sohda II as efficacious as compound 58, including one with no identified side effects or toxicity. And, as already noted, the authors of Sohda II recommended investigation of three other compounds, not compound 58.

Mosberg argues that the '200 and '779 Patents teach that Takeda "may" prefer to use the lower alkyls[71] and in particular a methyl (CH_3) or an ethyl (C_2H_5) as

70. Compounds 57 and 58 were reported in Sohda II to have the same effect on hypoglycemic activity (a score of 3), while compound 57 scored 2 and compound 58 scored 4 with respect to plasma triglyceride-lowering activity.

71. Alkyls are linear chains of carbon atoms singly bonded to other carbon atoms or hydrogen atoms.

substituents, and therefore it would not be surprising if Takeda used an ethyl substituent on a pyridyl ring. He relies on the Nohara Article and Sohda II as evidence that homologation was routine at Takeda. The test, of course, is not what Takeda might have tried, but whether one skilled in the art would have a reasonable expectation of success from synthesizing the homolog.

In any event, nothing in the '200 and the '779 Patents, or in any other publication from Takeda, would have given one skilled in the art an expectation of success from the substitution of an ethyl for a methyl. In its patents, Takeda specifically claims a variety of substituents on identified systems. For example, the '779 Patent includes substituents on a pyridyl or thiazolyl group, noting that "[a]s examples of such substituents may be mentioned lower alkyls (e.g., methyl, ethyl, etc.), lower alkoxy groups (e.g., methoxy, ethoxy, etc.), halogens (e.g., chlorine, bromine, etc.) and hydroxyl."

Finally, Mosberg points to specific illustrations in the '200 Patent that demonstrate to him that Takeda was aware that the substitution of a methyl with an ethyl "should be carried out to test for useful compounds." Again, this is not an opinion that there was any reasonable basis for an expectation of success. In any event, when the specific illustrations selected by Mosberg are actually examined, using the efficacy data on those same compounds as provided by Sohda II,[72] it

72. Mosberg cites to three sets of examples in the '200 Patent: compounds 3 and 4; compounds 5 through 9; and (Cont'd)

is immediately apparent that the prior art did not teach that the substitution of an ethyl for a methyl was likely to be beneficial. Sohda II shows a higher combined efficacy score for the methyl over the ethyl for one set, and an identical combined score for the methyl and the ethyl in the second set. The third set in the '200 Patent includes five compounds, but only three of the five are discussed in Sohda II. This set is a homologous series, with a CH_2 component repeatedly added. The Sohda II efficacy scores show no pattern, however, from the addition of the carbon atom.[73]

The position taken by Alphapharm's expert is perhaps best captured by his annotations to the expert report of Takeda's expert Danishefsky. On that report, he wrote in the margin that he agreed that a review of the biological effects of various substituents, as disclosed in the Sohda II article, made it clear that biological activity is "unpredictable." He added, "but this does not in [any]way make the choice of such analogs less obvious to try."[74] The test, of course, is not whether it is "obvious

(Cont'd)
compounds 15 and 16. In Sohda II, these are compounds 36 and 37; 38 to 40 (only three of the five are reported in Sohda II); and 11 and 14.

73. The compound in the middle of the series has the highest score.

74. Additional annotations by Mosberg indicate that he did not believe that there was any reasonable expectation of success from any particular modification of the molecule. He agreed that

(Cont'd)

to try" the synthesis of a particular compound, *see, e.g., In re O'Farrell,* 853 F.2d 894, 902 (Fed.Cir.1988), but whether one skilled in the art would have a reasonable expectation of success from doing so. At trial, the best the expert for Alphapharm could offer is that essentially anything can happen when one modifies a compound, so a change for the better might happen, and if it did, it would not be surprising. This does not come any closer to articulating a reasonable expectation of success.

In summation, Alphapharm's counsel tried with no success to limit the damage done by its expert's testimony. Admitting that there is inherent variability in the biological effects produced from even small changes in the structure of chemical compounds, he argued that a variation in the degree of an effect is entirely expected and is not surprising. He suggested that what would be surprising was to find an effect from the small change in the composition of a molecule in an entirely different body organ or system. Again, the issue is not whether something would be surprising, although the discovery that pioglitazone was non-toxic certainly qualifies as a surprising and unexpected event, but whether one could reasonably expect success.

(Cont'd)

"there is no data or information to even suggest that substitution of an ethyl for a methyl substituent would lead to predictable improvements in blood glucose or triglyceride lowering activity." Mosberg added in the margin, "there is no predictability only logical choice of analogs to try." As a final example, Mosberg notes in another annotation, that an effect on toxicity from small structural changes "can be neither expected nor unexpected. It would *not* be surprising."

In sum, even if compound (b) could have been identified by one skilled in the art as a lead compound worthy of further investigation, Alphapharm has failed to show that such a person would have had a reasonable expectation of success in synthesizing the pioglitazone molecule. Alphapharm has not shown that pioglitazone was prime facie obvious.

D. Objective Indicia of Non-Obviousness

1) Unexpected Results

Given Alphapharm's failure to show prima facie obviousness, there is no need for an extended discussion of the objective factors used to evaluate obviousness. For reasons already described, pioglitazone's non-toxicity was entirely unexpected. Compound (b) was a highly toxic compound, and nothing in the prior art would have led one skilled in the art to expect that the 5-ethyl on a 2-pyridyl ring would be non-toxic. As Alphapharm's Rosenberg admitted at his deposition, pioglitazone is "clearly superior" to compound (b) because of its non-toxicity.

There is one evidentiary issue that arose in connection with the issue of unexpected results that requires some discussion. Alphapharm offered evidence at trial that a long-term study of the effect of pioglitazone in dogs, conducted by Upjohn after Takeda had applied for what became the '777 Patent, suggested that pioglitazone may lead to an increase in heart size, and thus has some toxicity. An Upjohn scientist who testified

at trial discounted that interpretation of the test results. It is unnecessary to make any findings regarding this evidence, however, since it is entirely irrelevant to the issue of whether pioglitazone's non-toxicity, as disclosed in the '777 Patent, was an unexpected result.

Pioglitazone has, of course, been approved by the FDA and the defendants challenge Takeda's patent because they believe it is an effective and non-toxic drug that will be profitable for them to sell. As significantly, while it may be appropriate to use later-acquired evidence to bolster a finding of unexpected results,[75] to illustrate for instance that an invention is even more beneficial to mankind than was originally understood, *see Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed.Cir.2004), it is another thing altogether to suggest that after-acquired evidence should be used to undercut what appeared at the time of the patent application to be unexpected results. For instance, it would be entirely unfair to the patent applicant to discount what appeared at the time of an application to be unexpected results because our advancing and improved scientific knowledge allows us to understand why such results are to be expected. Therefore, as with all objective factors used to analyze the obviousness issue, after-acquired evidence of unexpected results should not be used to undermine a patent without a careful analysis of relevance. Here, the

75. There is, for example, strong evidence that the scientific community has come to understand that pioglitazone has a measurable and unexpected advantage over the other TZD on the U.S. market.

Upjohn tests, conducted long after the application for the '777 Patent, are irrelevant.

2) Additional Secondary Considerations

Evidence concerning other objective factors also shows that pioglitazone was a non-obvious invention. First of all, it is a huge commercial success. ACTOS® was launched in 1999, and by 2003 held 47% of the TZD market, as well as 9.9% of the total OAD market. In 2003, the gross sales of ACTOS® exceeded $1.7 billion. ACTOS® is the embodiment of pioglitazone, the invention disclosed in the '777 Patent, and therefore this commercial success can presumptively be attributed to the invention itself.

Pioglitazone also responds to a long felt but unmet need in the market of pharmaceutical treatments of diabetes. The introduction of TZDs, led by Rezulin® in 1997, revolutionized the care of diabetes. Rezulin®, however, has been removed from the U.S. market due to issues associated with liver toxicity, and today, only ACTOS® and Avandia® are available. Out of the millions of TZDs, only these two have been found to be safe and effective to treat insulin resistance in the muscle.

Alphapharm presents several arguments in a futile effort to undermine Takeda's compelling objective evidence of non-obviousness, particularly its evidence of commercial success. While Alphapharm concedes that there is evidence both of commercial success and that the successful product is claimed in the patent, it argues

that other factors serve to undercut "the prima facie case of nexus" between the commercial success and the claimed invention.

Alphapharm argues that much of the commercial success of ACTOS® is due to events that were unforeseen at the time that the '777 Patent issued, such as the withdrawal of Rezulin® from the market, and an unexpected rise in obesity with an accompanying increase in the incidence of diabetes.[76] These arguments miss the mark. There is no requirement that the invention be the only successful product in its market niche or the most successful. Moreover, ACTOS® would have been an important and successful invention by any reasonable measure even if the incidence of diabetes had remained unchanged since the time of the invention.

Alphapharm also argues that Takeda's success is more attributable to its marketing efforts, particularly its partnership with Eli Lilly, than the inherent value of the invention. This argument flies in the face of the strong evidence from medical practitioners about the benefits and the perceived benefits of ACTOS®. In any event, Takeda and GlaxoSmithKline invest roughly the same amount of money in their efforts to market their two TZD products, and both drugs have found success.

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76. There is no need to explore the extent to which the perceived rise in obesity and diabetes is due to a redefinition of obesity in 1998, and a change in the diagnostics for diabetes in 1997.

Finally, Alphapharm argues that Takeda's prior art patents, particularly the '200 and '605 Patents, undermine the nexus between ACTOS®' commercial success and the non-obviousness of the '777 Patent. The suggestion is that because Takeda had the right to exclude others from making the closest prior art compounds, the ability of other companies to enter the TZD market was stifled.[77] The argument is completely specious. Alphapharm has not shown that any of the compounds disclosed by Takeda in its patents were viable candidates for commercial development. Takeda's competitors had every opportunity to develop new compounds that were improvements over the compounds Takeda disclosed. This is exactly what Sankyo did in developing troglitazone, the active ingredient in Rezulin®. The patent that protects troglitazone lists the '605 and '902 Patents as prior art. The fact that only one other company has a TZD in the market today, despite the commercial opportunities available for an effective insulin sensitizer, is strong secondary evidence of pioglitazone's non-obviousness.

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77. In making this argument, Alphapharm relies on *Merck*, 395 F.3d at 1377, but in doing so, reads the case far too broadly. In *Merck* the patent at issue was a method claim for the use of a particular compound, which was protected by a patent owned by Merck. *Id.* at 1366. Because Merck owned the underlying patent, and thus could prevent others from commercially developing the method of use at issue, the court found that the "chain of inferences fails on these facts." *Id.* at 1377. The case does not establish that commercial success is not probative simply because a patent holder also holds a prior art patent.

In sum, Alphapharm has not carried its burden of showing that the invention of pioglitazone was obvious. It has searched for a theory of obviousness, and its efforts have proven futile with each iteration of a theory.[78] Alphapharm's Section 355 Statement did not articulate a successful theory of obviousness, and its efforts to create one through the direct testimony of its expert, and yet another one as the trial unfolded all failed. Nothing in the prior art would have given one skilled in the art any reasonable expectation that the creation of pioglitazone would result in the discovery of an anti-diabetic treatment that was efficacious and non-toxic.

II. Inequitable Conduct

Mylan contends that the '777 Patent is invalid because Takeda engaged in inequitable conduct. Applicants for patents are bound by a duty of "candor and good faith" to the PTO. *Purdue Pharma L.P. v. Endo Pharm. Inc.*, 04-1189, 04-1347, 04-1357, 2006 WL 231480, at *4 (Fed.Cir. Feb.1, 2006).[79] Included in the duty is the

78. It is telling that two of the defendants never sought to attack the '777 Patent on the ground that it was obvious, and a third defendant abandoned the theory of obviousness it had articulated in its own Section 355 Statement.

79. The conduct of applicants while applying for patents is governed by 37 C.F.R. § 1.56 ("Rule 56"), which is promulgated by the PTO pursuant to 35 U.S.C. §§ 6 and 131. *See Molins PLC v. Textron, Inc.*, 48 F.3d 1172, 1179 n. 8 (Fed.Cir.1995). The governing standard for evaluating defendant Mylan's claims of (Cont'd)

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inequitable conduct is the regulation as it stood in 1986, when Takeda pursued its application for the invention covered by the '777 Patent. *See id.* In 1986, the regulation read in relevant part:

> (a) A duty of *candor and good faith* toward the Patent and Trademark Office rests on the inventor, on each attorney or agent who prepares or prosecutes the application and on every other individual who is substantively involved in the preparation or prosecution of the application and who is associated with the inventor, with the assignee or with anyone to whom there is an obligation to assign the application. All such individuals have a duty to disclose to the Office information they are aware of which is material to the examination of the application. Such *information is material where there is a substantial likelihood that a reasonable examiner would consider it important* in deciding whether to allow the application to issue as a patent. The duty is commensurate with the degree of involvement in the preparation or prosecution of the application.
>
> (d) No patent will be granted on an application in connection with which fraud on the Office was practiced or attempted or the duty of disclosure was violated through *bad faith or gross negligence.* The claims in an application shall be rejected if upon examination pursuant to 35 U.S.C. 131 and 132[sic], it is established by *clear and convincing evidence* (1) that any fraud was practiced or attempted on the Office in connection with the application, or in connection with any previous application upon which

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obligation of applicants to disclose information of which they are aware that is "material to the examination of the application." 37 C.F.R. § 1.56(a) (1985). The duty encompasses an "affirmative misrepresentation of a material fact, failure to disclose material information, or submission of false material information." *Purdue Pharma,* 2006 WL 231480, at *4, 438 F.3d at 1128. Materiality and intent "must be shown by clear and convincing evidence." *Id.* The burden of proof required to prove inequitable conduct has been described as a "heavy burden". *Hoffmann-La Roche, Inc. v. Promega Corporation,* 323 F.3d 1354, 1359 (Fed.Cir.2003)

For patents prosecuted before 1992, "information is material where there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application as a patent." 37 C.F.R. § 1.56(a); *see Dayco Products, Inc. v. Total Containment, Inc.*, 329 F.3d 1358, 1365 (Fed.Cir.2003). Materiality is not limited to matters reflected in the claims of the patent, *PerSeptive Biosystems, Inc. v. Pharmacia Biotech, Inc.*, 225 F.3d 1315, 1322 (Fed.Cir.2000), but embraces "any information that a reasonable examiner would substantially likely [sic]

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> the application relies, or (2) that there was any violation of the duty of disclosure through bad faith or gross negligence in connection with the application, or in connection with any previous application upon which the application relies.

37 C.F.R. § 1.56(a), (d) (1985) (emphasis supplied).

consider important in deciding whether to allow an application to issue as a patent." *Dayco Products,* 329 F.3d at 1368 (citation omitted); *see Akron Polymer Container Corp. v. Exxel Container, Inc.,* 148 F.3d 1380, 1382 (Fed.Cir.1998). The standard for materiality is not a "but for" standard. *Merck & Co. v. Danbury Pharmacal, Inc.,* 873 F.2d 1418, 1421 (Fed.Cir.1989); *see also Digital Control Inc. v. Charles Mach. Works,* 05-1128, 2006 WL 288075, at *7 (Fed.Cir. Feb.8, 2006). It is not necessary to find that an examiner relied on the misrepresentation or omission at issue, only that it would have been "within a reasonable examiner's realm of consideration." *Hoffmann-La Roche, Inc.,* 323 F.3d at 1368 (citing *Merck & Co.,* 873 F.2d at 1421). Affidavits submitted to the PTO may be "inherently material." *Digital Control,* 2006 WL 288075, at *8, 437 F.3d at 1318; *see also, Refac Intern., Ltd. v. Lotus Development Corp.,* 81 F.3d 1576, 1583 (Fed.Cir.1996).

Direct evidence of intent to deceive is "rarely available", but intent "may be inferred from clear and convincing evidence of the surrounding circumstances." *Purdue Pharma,* 2006 WL 231480, at *9, 438 F.3d at 1134 (citation omitted); *see also Ferring B.V. v. Barr Labs., Inc.,* 05-1284, 2006 WL 335601, at *8 (Fed.Cir. Feb.15, 2006). While a "court must weigh all evidence, including evidence of good faith" in determining intent, "a patentee facing a high level of materiality and clear proof that it knew or should have known of that materiality, can expect to find it difficult to establish 'subjective good faith' sufficient to prevent the drawing of an inference of intent to mislead." *Purdue Pharma,* 2006 WL 231480, at *9, 438 F.3d at 1134 (citation omitted).

Appendix B

If the duty is breached in a way that is both material and intentional, then the patent will be invalidated if "the equities warrant a conclusion that inequitable conduct occurred." *Id.* at *4, 438 F.3d at 1128. The material misrepresentations or omissions must be "sufficiently serious in light of the evidence of intent to deceive, under all the circumstances, to warrant the severe sanction of holding the patent unenforceable." *Hoffmann-La Roche,* 323 F.3d at 1372.

Mylan has failed to carry its heavy burden of showing that Takeda engaged in inequitable conduct. Mylan principally claims that Takeda intentionally made material misrepresentations in its presentation of the comparative test results for the six compounds listed in Table 1 of the '777 Patent, and that Takeda should have added information concerning a seventh compound to the table.

There are many indicia of Takeda's good faith in its application to the PTO in 1986. First, with the exception of two test results it obtained in response to the Office Action, the test results Takeda presented to the PTO in Table 1 were drawn from reports that Takeda and its research partner Upjohn had used in 1984 to select five compounds, including pioglitazone, for further research and potential development as a pharmaceutical. Takeda had every incentive to reflect in those reports its best judgment about what the test results showed so that the companies' money and the scientists' energies would be spent as productively as possible. There is simply no basis to find that there was any misrepresentation in

the 1984 reports, much less any incentive to misrepresent test data.

Second, Takeda identified the relevant prior art to the PTO. Both Sohda II and the '200 Patent were described. In addition, the chemical structure for the closest prior art-compound (b) on Table 1, which is compound 58 in Sohda II-is set out in a diagram so that it can be easily compared to the chemical structure for pioglitazone and the other compounds listed in Table 1.

Third, Takeda did not manipulate the data presented in Table 1 to make pioglitazone appear better than its internal data reflected. For example, Table 1 shows that compound (b) is superior to pioglitazone in the reduction of both blood glucose and triglycerides. Even when the Office Action required Takeda to fill in three more data points in Table 1-the triglyceride data for rats for compounds (c), (d) and (e)-Takeda gave the PTO figures that were comparable to or superior to the figures for pioglitazone in Table 1.[80]

Fourth, Takeda had powerful additional evidence of the superiority of pioglitazone over the prior art which it did not present to the PTO. Report A-15-34 reflects the results of the in vitro chick lens assay[81] for many

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80. Pioglitazone ED^{25} value for lowering rat triglyceride levels was shown as 3; the comparable values for compounds (c), (d) and (e) were reported as 6, 4 and 2, respectively.

81. It was this test which had resulted in the abandonment of ciglitazone as a marketable pharmaceutical.

compounds, including those in Table 1. Only pioglitazone and compound (e) of the six compounds listed in Table 1 showed no evidence of toxicity in this test. This was additional evidence of the superiority of pioglitazone over the compound in the prior art to which it was most structurally similar, compound (b), which Takeda had at hand to share with the PTO if necessary.

Fifth, there is no dispute about the superiority of pioglitazone over compound (b), the only prior art compound in Table 1. Mylan cannot explain how Takeda could have anticipated in 1984, when it created Reports A-15-13 and A-15-34, that information about compounds (c), (d) or (e) would be included in the PTO application or what additional explanations the examiner would seek in an Office Action.

Ignoring this powerful evidence that Takeda acted in good faith in its presentation to the PTO, Mylan has cobbled together a series of arguments in an effort to show inequitable conduct. As noted, its arguments relate to the presentation of data in Table 1. It emphasizes data concerning two compounds: compound (c), which is the 5-methyl homolog of pioglitazone, and compound 3894, which is the unsubstituted pyridyl ring. With respect to compound (c), Mylan contends that Takeda misrepresented the data regarding compound (c)'s potency to make it appear weaker than pioglitazone. It points out that compound (c) had no toxicity indicated on Table 1, and therefore, pioglitazone would not have appeared superior to compound (c) if their efficacy

numbers were presented as comparable.[82] With respect to compound 3894, Mylan argues that Takeda had a duty to report the comparative test results for this compound on Table 1, but did not. Compound 3894 had comparable if not better efficacy than pioglitazone, but was rejected for development by Takeda due to its toxicity to the heart. In addition, as described below, Mylan raises a few other issues to attack Taeda's honesty in its presentation of Table 1 data.

Before addressing Mylan's categories of alleged misrepresentations, a few observations are in order. Many of Mylan's examples of the misrepresentation or omission of data rest on testing data it culled from surviving Takeda notebooks that were produced in discovery in 2004 and 2005. The screening tests were conducted approximately 20 years earlier, and not all of Takeda's laboratory notebooks have survived. Thus, Mylan's analysis rests on the fallacy that it has a complete set of the testing data from which to judge the completeness and fairness of the presentation of the testing results to the PTO.

There is a second flaw in Mylan's contention that Takeda should have used the experimental data lifted directly from the notebooks rather than the data in the reports on which Takeda and Upjohn relied to make their research decisions. Presenting raw, unanalyzed data from notebooks would have been both incomprehensible to an examiner and misleading. Indeed, the notebooks

82. Compound (c) failed the chick lens assay test, but those data were not presented to the PTO.

contain some test results for pioglitazone that are more favorable than those listed on Table 1 and test results for some of the other compounds that are less favorable than the descriptions of those compounds on Table 1.

Fujita analyzed all of the test results in 1984, and chose to include in Report A-15-34 those that he considered the most reliable. Takeda and Upjohn relied upon the data in that report in making critical business decisions, and it was entirely appropriate for Takeda to rely on that same data in preparing Table 1 for the PTO.

With two exceptions, which are discussed below and concern the strain and age of rats, Mylan has failed to show that there was any misrepresentation or material omission in Takeda's presentation of data. With respect to the two errors, Mylan has failed to show that the errors were either material or the result of any intentional misconduct by Takeda.

A discussion of Mylan's specific contentions follows. Its contentions are organized according to the column in Table 1 to which they relate. Its arguments concerning compound 3894-the compound not included on Table 1-are addressed last.

A. Misrepresentations

1) Mouse ED^{25} values

Mylan argues that most of the ED^{25} values for the lowering of blood glucose and plasma triglycerides in

mice that were reported in Table 1 were false and misleading, and that the actual test results obtained by Takeda were not reported to the PTO. In particular, Mylan stresses data obtained in a single 1983 experiment in which pioglitazone and compound (c) were tested together or head to head,[83] and shown to have roughly the same ED^{25} values, while Table 1 reflects pioglitazone significantly outperforming compound (c) in these measures.[84]

As already noted, the ED^{25} mouse data in Table 1 is identical to that contained in Report A-15-34. Mylan's assertion that there was a misrepresentation is based exclusively on the results of a handful of experiments Mylan located in surviving Takeda notebooks. There were many more experiments conducted by Takeda than are reflected in the surviving notebooks. Indeed, as has been explained previously, because there were so many screening tests performed, for many compounds Report A-15-34 presents a range of test results for the efficacy

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83. Mylan makes a similar argument for compound (e), claiming that data from a single experiment in a Takeda notebook shows that compound (e) outperformed pioglitazone. For the reasons discussed in the analysis of the argument concerning compound (c), Mylan has not shown that a misrepresentation occurred in the presentation of the ED^{25} mice data on Table 1.

84. Table 1 showed ED^{25} blood glucose and triglyceride lowering scores of 6 and 6 for pioglitazone, but 20 and 20 for compound (c). In the single experiment to which Mylan points, the comparable pioglitazone values were 5.2 and 14, but 6.4 and 18 for compound (c).

testing. It first lists the figure which Fujita selected as the most reliable, and then in parentheticals gives a range of test results.[85]

It was entirely appropriate, and indeed necessary, for Fujita to apply his professional judgment to the mass of test results and select the test results on which he felt that Takeda and Upjohn could best rely in the Fall of 1984. Not all tests yield similarly reliable data. Some of the test results from the Takeda notebooks on which Mylan has relied are preliminary two dose tests, which would not yield reliable ED^{25} data. In other tests it appears that the effective dose is beyond the administered doses, and again would not be a reliable basis for determining the effective dose. In other surviving tests, where there does not appear to be any particular defect in the test, Mylan still has not shown that those data should have been used in Table 1 instead of the data Takeda chose to present there.[86] Without

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85. For instance, the ED^{25} blood glucose data for compound (c) were reflected in Report A-15-34 as: "20 (2-5)". The data in the parenthetical represent the relative potency of compound (c) to ciglitazone, ciglitazone being accorded a rating of one. Fujita chose the test reflecting an ED^{25} value of 20 as the most reliable test, but by including the data in the parenthetical, reflected that the test results ranged from values between 8 and 20. Ciglitazone had an ED^{25} value of 40 in Report A-15-34.

86. Using the notebook data to create ED^{25} values, and after eliminating tests where only two doses were administered or where the dose response curve was flat (indicating that the ED^{25} value was beyond the range of doses tested), the data currently

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having all of the underlying test results from which Fujita selected the most reliable tests to calculate the ED^{25} values contained in Report A-15-34, it is simply impossible today to reconstruct why any single test was or was not chosen as the most reliable. What can be established today with confidence, however, is that Fujita had every motive to use his best judgment in 1984 in compiling the data for Report A-15-34, and it was those data which were presented to the PTO in 1986.

In this connection it is important to note that Takeda had given over fifty compounds to Upjohn, as well as KKA mice, so that Upjohn could replicate the efficacy testing that Takeda was doing in its own laboratories. Two scientists who were deeply involved in the 1984 diabetes drug program at Upjohn testified at trial and confirmed that Upjohn not only did its own efficacy testing but also that all of the results it obtained were consistent with the results that Takeda reported. These two scientists, neither of whom has any stake in this litigation, spoke highly of the competence and integrity of the Takeda scientists and its testing program. The existence of Upjohn's parallel testing program is yet another reason to find that Fujita used his best judgment in choosing the efficacy numbers (and other data) for Report A-15-34. Upjohn's scientists were in a position

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available results in an identical ranking of pioglitazone, and compounds (a) and (c) to that presented to the PTO: pioglitazone was superior to compound (c); compound (a) had the poorest performance. There was insufficient surviving data for the other compounds to do a meaningful comparison.

to disagree with his presentation of the data, and Fujita knew that.[87]

There are two additional arguments that Mylan makes about the presentation of the efficacy scores in Table 1 for mice. It points to comparisons with ciglitazone that were contained in monthly internal reports at Takeda in early 1984, and Report A-15-13, circulated in February 1984. These comparisons listed compounds that screening tests had determined were "five times as potent as ciglitazone." Pioglitazone and compound (c) were among the compounds found as having such a superior performance. Mylan argues that it is inconsistent to identify compound (c) as five times more potent than ciglitazone in these internal documents, and yet to list it on Table 1 as only two times as potent.[88]

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87. In a chapter of a book published in 1990, the Upjohn scientists who testified at trial described research into ciglitazone, pioglitazone and other TZDs. They reported that Takeda discovered through its research that replacing the left hand moiety of ciglitazone with a 2-pyridinylethoxy produced compounds "approximately 5-10 times more potent than ciglitazone". They added that further testing of the compounds for efficacy and safety resulted in the selection of pioglitazone for development. Despite Mylan's arguments to the contrary, nothing in this general description of the Takeda screening program undermines the reliability of Report A-15-34, a report on which these same Upjohn scientists relied to make research decisions.

88. On Table 1, ciglitazone's ED^{25} values for lowering blood glucose and triglyceride levels in mice are both 40, while compound (c)'s are listed as 20.

Appendix B

Takeda's early screening tests were part of a program to find more potent and less toxic compounds than ciglitazone. They created new compounds, including compounds (c), (d) and (e) in mid-1983, and subjected them initially to two-dose tests, and those that survived that screening, to three-dose tests. During 1984, Takeda continued to test compounds. For the reasons already explained, there is no reason to doubt that Takeda used its best judgment in selecting the most reliable potency values for Report A-15-34 from among the universe of available test results,[89] and those same numbers appear in Table 1. Mylan has not shown that Takeda engaged in inequitable conduct by failing to give the PTO data reflecting the best performance by a compound, instead of the performance judged by extremely well qualified scientists as the most reliable performance.[90]

Finally, Mylan finds in another section of Report A-15-34 support for its argument that Table 1 was

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89. As already noted, Report A-15-34 did include a range of potency, comparing each compound's potency to ciglitazone, and compound (c)'s range of potency was listed in Report A-15-34 as "2-5" or two to five times as potent as ciglitazone.

90. Mylan has argued that Takeda should have given the PTO the range of test results reflected in the parentheticals in Report A-15-34. Mylan has not shown that the range of results would have been material to the examiner or anything other than an additional layer of detail that was unnecessary for the examiner to perform his function. Giving the PTO the most reliable test data, as opposed to a summary of all test results was sufficient to meet Takeda's obligations to the PTO.

misleading. In Figures 5 and 6 of Report A-15-34, pioglitazone is shown as somewhat more potent in mice, and as creating less "brown fat" in rats, than compound (c).[91] Pioglitazone is not shown in these figures, as it is in Table 1 of Report A-15-34 (and in Table 1 of the patent), as over three times more potent than compound (c). Takeda apparently chose to use some of the test results for compound (c) in these figures that were different from the values it chose as the most reliable when it created Table 1 of Report A-15-34.

Mylan has not shown that Takeda should have presented the data used to create the two figures in Report A-15-34 instead of the Table 1 data to the PTO. The two figures do not even have numbers associated with a particular compound; the figures are simply graphs composed of points entered on a logarithmic scale. One can only estimate, and very roughly at that, what the underlying values are. The only reliable *numbers* in Report A-15-34 are those that were reported to the PTO.

Takeda's testing, which was extensive, was nonetheless preliminary, screening testing, used to identify a small group of compounds, ultimately five, for more intensive testing and potential development. Takeda was under no obligation to conduct more

91. Takeda created a graph of the data using these two parameters and from that graph formed the hypothesis that the increase in the brown adipose tissue ("brown fat") in the rats may be partially due to the pharmacological potency of a compound.

extensive testing before applying for a patent; its only obligation was to present its results as of that time honestly. Mylan has not shown that Takeda violated that obligation in connection with the mouse efficacy data.

2) Rat ED^{25} values

Mylan argues that some of the ED^{25} values for plasma triglyceride lowering that Takeda obtained from testing rats were not obtained in the manner Takeda described to the PTO in the '777 Patent application and the Amendment, and that Takeda concealed some of the results it did obtain from its testing.[92] Mylan makes three separate arguments, but has not shown in connection with any of them that Takeda engaged in inequitable conduct.

a) ED^{25} value for pioglitazone

Relying again on surviving notebook data, Mylan argues that Takeda misrepresented the ED^{25} in rats for pioglitazone. Table 1 reported the value as 3 for pioglitazone, but Mylan points to data from tests reflected in surviving notebooks that show different values, one of them lower than a 3.[93] For the reasons already discussed, Mylan has not shown that there was

92. In its summation, Mylan only mentioned one of these three issues: the failure to tell the PTO that a control animal had been excluded from an experiment.

93. The ED^{25} values identified by Mylan for pioglitazone are 17.9, 7.8 and 2.3.

any misrepresentation by Takeda. Takeda took the figure for pioglitazone from Report A-15-34, and that was a reliable source of data to present to the PTO.

b) Exclusion of a control animal

Mylan argues that Takeda misrepresented its testing protocol to the PTO when it indicated that there were five rats in each testing group, including the group of animals used as a control. Mylan argues that Takeda should have advised the PTO that in one test it had omitted test data obtained from one control animal.[94]

In responding to the Office Action, Takeda conducted experiments to obtain ED^{25} values for plasma triglyceride lowering in rats for compounds (c), (d) and (e). One of the five animals in the control group gained comparatively little weight during the test period and had anomalous readings for other pertinent characteristics.[95] In averaging the data obtained from the control group in this test, a Takeda researcher chose to eliminate the readings from this one animal.

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94. Mylan initially argued that Takeda should not have eliminated the control animal from its calculations since the censoring of the animal dramatically altered the test results. It appears to have abandoned this argument. As explained above, the censoring was entirely appropriate.

95. The control animal had an elevated NEFA level (non-esterified fatty acids), which indicated that it was either not sufficiently eating or assimilating its food.

Appendix B

The "censoring" of animals in biological testing is encouraged where results are not representative and where inclusion would be misleading. The exclusion of one control animal was entirely appropriate here and reflects the exercise of sound scientific judgment. Scientific publications do not always report the exclusion of one laboratory animal in their description of test results, and there is no basis to find that it should have been reported to the PTO or that the test results should have included the readings obtained from this single animal.

Mylan also argues that Takeda's statement in the Amendment about control group values was misleading because it did not explain that an animal had been censored in one experiment. In the Office Action, the examiner expressed uncertainty about how to interpret the Table 1 data, noting *inter alia* that the disclosure failed to provide "values for the control group." In response, Takeda explained that

> Each control value of blood glucose and TG is determined to be 100% and that of "liver weight", "heart weight" and "number of erythrocyte" is estimated to be zero % from the above numerical expressions. Therefore it is *meaningless to show the values of the control.* The disclosure of the table . . . is sufficient for those skilled in the art to interpret the data.

(Emphasis supplied).

Appendix B

Takeda's response to the examiner's inquiry was entirely accurate. It explained why one skilled in the art would understand all control values to be 100%, and the performance of a compound to be measured against that assumed control value. This explanation helped the examiner to read Table 1; it did not concern the particular experiment in which an animal was censored or even the circumstances more generally in which one animal would be censored in order to obtain a reliable test result. Mylan has not shown that there was any misrepresentation or material omission.

c) ED^{25} data for compound (d)

As noted, the Office Action requested that Takeda provide triglyceride effectiveness data for compounds (c), (d), and (e). These were the only three fields of data not completed in Table 1 as it was originally presented to the PTO. When the supplemental testing done to respond to the Office Action demonstrated no triglyceride-lowering activity in compound (d), Fujita lifted the results from Report A-15-34 and reported a "4" as the ED^{25} value, a number close to the value of "3" reported for pioglitazone. Ciglitazone's value was "70".

Mylan has not shown that there was any effort to mislead the PTO by reporting a "4" for compound (d). If Takeda had reported that compound (d) had no potency, rather than fairly strong potency, then Mylan may have had grounds to complain. As it was, what Takeda did was utterly inconsistent with any effort to place pioglitazone in a more favorable light than it deserved.

Appendix B

3) Toxicity in Rats

Mylan has argued that Takeda misled the PTO by falsely describing the strain and age of rats that it used to obtain toxicity data.[96] It has failed to show inequitable conduct in either instance.

a) Strains of rats

The studies measuring the potency of compounds were performed in Sprague-Dawley rats, while the toxicology tests were performed in Wistar rats. Takeda represented to the PTO that all of the testing had been performed in Sprague-Dawley rats.[97] Mylan has not shown that this error was material.

Two of the most common strains[98] of laboratory rat

96. It is not entirely clear if Mylan continues to press these arguments. Mylan did not mention either of these issues in its summation.

97. The '777 Patent described the experimental process for obtaining data regarding lipid lowering activity and toxicity in rats. The patent represented that the former tests had been conducted with "[m]ale Sprague-Dawley rats" and the latter with "[m]ale and female Sprague-Dawley rats."

98. A strain is a group of individuals who share a presumed common ancestry and have clear-cut physiological, but not usually morphological, distinctions. Wistar and Sprague-Dawley rats are both outbred strains, meaning that they are maintained as colonies of animals of unidentified genotype. Individual

(Cont'd)

used in toxicology studies are Wistar and Sprague-Dawley. Both strains are of healthy animals, and toxicology assays are almost always performed in healthy animals in order to rule out other causes of abnormalities.[99] The Sprague-Dawley strain originated from crosses with Wistar females and remains genetically similar to the Wistar today. Indeed, there are still no genetic markers to differentiate the two strains. Credible expert testimony established at trial that the use of Wistar rats instead of Sprague-Dawley rats did not change the reliability of the conclusions that were presented to the PTO since the same strain was used across the toxicology experiments.[100] There is simply no basis to find that the error was material or made as a result of an intent to mislead.

(Cont'd)
animals from an outbred stock may differ markedly in their genetic characteristics. In contrast, due to cross-breeding of brother-sister pairs in inbred strains over many generations, individuals within an inbred strain are treated as genetic clones.

99. Three dose effectiveness tests were done in normal Sprague-Dawley rats to obtain plasma triglyceride levels. If the levels of treated animals were reduced, that was an indicator of the compound's antidiabetic activity.

100. For example, when two-week toxicity studies were done in both Wistar and Sprague-Dawley rats for pioglitazone, the results were essentially equivalent.

b) Safety margin analysis

Mylan argues that the value of the safety margin analysis that Takeda developed in response to the Office Action is undercut by the fact that Takeda used Sprague-Dawley rats for its efficacy data, but Wistar rats for the toxicity testing. This argument reflects a fundamental misunderstanding of the testing process. Since the same strain of rat was used as both the control animal and the animal receiving the compound in any given experiment, the efficacy data and the toxicity data were each derived from a scientifically sound experiment. Scientists commonly derive safety margin data using two different animal models. Again, Mylan has not shown that there was any failure to provide the PTO with information material to the examiner.

c) Age of rats

The '777 Patent and the Declaration both explain that the toxicity studies in rats were two-week tests done in rats that were "5 weeks old". In one of the two-week toxicology studies, however, the one in which pioglitazone itself was tested, at the initiation of the study the rats were six weeks of age.[101] Since the results were based on normalized weight calculations and a comparison to control groups of the same age as the test groups, the error in describing the age of the rats was immaterial.

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101. Pioglitazone and compound 3894 were tested in rats at least six weeks old. The compounds listed on Table 1 other than pioglitazone were tested in rats five weeks old.

Mylan argued at trial that testing pioglitazone in animals that are one week older gave it an advantage because rats at that age are going through puberty and as more mature and bigger animals will be less susceptible to the toxic effects of the compounds. The credible scientific evidence at trial established that this small difference in age at the point in which the tests began had no effect on the validity of the test results.[102]

Puberty is a process and individual rats generally enter this process at any time between thirty-five to sixty days, that is, between five to eight and a half weeks. Tests conducted on rats that are from five to seven weeks old and from six to eight weeks old are thus each conducted on rats presumptively undergoing puberty. Using control animals of the same age and normalizing organ weights to body weight, which Takeda did for each test, are sufficient to eliminate any variations of significance among the tests.

B. Omission: Compound 3894

Mylan argues that Takeda had an obligation to disclose to the PTO activity and toxicity data regarding compound 3894, a compound revealed in the prior art,

---

102. Even though Alphapharm purported to be pursuing an obviousness claim, it chose to cross-examine Takeda's expert on the issue of the age of the rats, using a series of graphs it prepared based on data drawn from Takeda's test results. Correctly interpreted, the graphs in fact underscored the expert's opinion that the one week age difference had no impact whatsoever on the test results.

specifically in Sohda II. Compound 3894 is a TZD molecule with a 2-pyridyl ring at the left end, but no substituents on that ring. It is the parent structure for the left hand moiety of the pioglitazone molecule. Mylan argues that if Takeda had revealed that compound 3894 had a comparable activity and toxicity performance to pioglitazone then the PTO "may" have concluded that pioglitazone was not patentable over prior art. Put another way, Mylan argues that Takeda falsely asserted to the PTO that the introduction of an ethyl group to the 2-pyridyl ring produced unexpected results because it knew that pioglitazone is not superior to compound 3894.

In the '777 Patent Takeda made the following statement:

> As is apparent from the experimental results given in Table 1, Compound (I) of this invention is superior to the compounds (a), (c), (d) and (e) and comparable to the compound (b) in hypoglycemic and hypolipidemic activities, while showing extremely low toxicity as compared with the compounds (a), (b), (d) and (e). *Such an effect as above caused by the introduction of an ethyl group is quite unexpected.*

(Emphasis supplied.)

Compound 3894 is toxic. As reflected in Reports A-15-13 and A-15-34, two-week toxicity tests performed in rats demonstrated a statistically significant toxicity to

the heart known as cardiomeglia or enlargement of the heart. Mylan has not shown either that Takeda should not have relied on the results reflected in Report A-15-34 in making judgments about the unexpected results achieved through the introduction of an ethyl group, or that the underlying test results on the toxicity of compound 3894 were unreliable.[103]

Mylan points to Takeda documents in which the effects on the heart by compound 3894 were described as "weak" or "mild", as well as Report A-15-13 from February 2004, where this compound was described as one of four compounds that appeared less toxic than the others that had been tested as of that time, and which because of their potency, appeared "much easier to continue further studies including clinical trials." These preliminary views are insufficient to overcome the compelling evidence that as of the Fall 2004, when Report A-15-34 was prepared and Takeda and Upjohn made their judgments about what toxicity levels would be disqualifying and which compounds warranted further testing, compound 3894 was disqualified because of its toxicity.

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103. Mylan first suggested that the statistical significance of the toxicity finding needed to be confirmed through an analysis of variance or ANOVA, with a Dunnett's post-test. Mylan, however, did not perform that test, and when Takeda's expert did, the testing confirmed Takeda's finding of statistical significance. Mylan's expert then speculated that the testing results might be an "artifact". He suggested that the results be confirmed through retesting, but Mylan undertook no such testing.

Appendix B

As already discussed in connection with the discussion of the issue of obviousness, the closest prior art to pioglitazone was compound (b), not compound 3894.[104] Moreover, it was important to compare pioglitazone to ciglitazone, which had advanced as far as human trials before it had to be abandoned because of toxicity. It was unnecessary for Takeda to present testing data for compound 3894 as well. By presenting the comparison with compound (c), Takeda was presenting data with its methyl-substituted homolog, which was more closely related to pioglitazone in its chemical structure than the unsubstituted compound 3894.

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104. By the time of its summation, Mylan had abandoned any claim that compound 3894 was the closest prior art. It argued that *In re Johnson*, 747 F.2d 1456 (Fed.Cir.1984), requires an applicant for a patent to present information about any relevant prior art, even if it is not the closest prior art. *Johnson* reaffirms that an applicant must compare the invention to the closest prior art. *Id.* at 1461. That was done here. *Johnson* also addresses the duty of comparison where there are two equally close references. *Id.* That is not an issue presented here.

One Mylan expert had asserted without any analysis that compound 3894 was the closest prior art, but admitted on cross examination to each of the facts on which Takeda's far more impressive and careful expert relied in forming his conclusion that a substituted pyridyl, such as compound (b), is closer structurally to pioglitazone than an unsubstituted pyridyl. To give but one example, the introduction of an alykyl substituent changes the shape of the TZD molecule dramatically, which can have profound effects on the interface between the TZD and the PPAR-gamma molecules.

C. Intent

It is undisputed that Takeda made two misstatements of fact to the PTO. Takeda erred in describing the strain and age of rats used in the toxicity testing. Neither of these errors was material. Mylan has failed to show that Takeda made any other misstatements or failed to provide the PTO with material information. In any event, Mylan has utterly failed to show that Takeda ever acted in bad faith in the prosecution of the '777 Patent.

The evidence of Takeda's good faith is abundant. Takeda's lead scientist for this project was Fujita. As the Chief Scientist of the Biology Research Laboratory, he had ultimate responsibility for the conduct of the screening tests run in 1983 and 1984; he chose the efficacy values for Report A-15-34; and he recommended pioglitazone as one of the twelve compounds from which Takeda and Upjohn should select their candidates in October 1984 for more intensive studies and possible development as a pharmaceutical. He did not include either compound 3894 or any other Table 1 compound among that group of twelve. Fujita has long since retired from Takeda, but he testified at trial. He was an entirely credible witness. Despite extensive cross-examination, he remained a patient, careful witness who worked hard to give precise, accurate answers to every question that he was asked. Although he had no current recollection of many of the details of events from the mid-1980s, his testimony established beyond peradventure that he had used his best scientific judgment and considerable

expertise at that time. He is, in short, an honorable man and distinguished scientist. There is absolutely no evidence that he ever acted with intent to deceive either other scientists at Takeda or Upjohn in preparing Report A-15-34 or the PTO.

Fundamentally, Mylan has never been able to overcome the hurdle presented by the fact that Takeda's work was undertaken in collaboration with Upjohn, and that the Table 1 data were taken directly from Report A-15-34. Even if his character would have permitted him to act other than with complete scientific integrity, Fujita had no *motive* to use anything other than his best judgment in creating Report A-15-34. He had no way to know what results Upjohn had obtained in testing these same compounds and whether its judgments would agree with his own, and he certainly had no ability to anticipate what data might be important in any future PTO proceedings. As significantly, he had no motive to fabricate data for compounds such as compound (c) that were not even in the prior art.[105] Fujita's only identifiable motive was to choose as wisely as he could the most promising compounds into which Takeda and Upjohn would invest significant resources to determine if they had successfully identified an efficacious, safe compound for use as a pharmaceutical. To place Mylan's argument

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105. If, for instance, compound (c) had been a better choice for pharmaceutical development than pioglitazone, then Takeda would have had no reason not to select compound (c) for development. It certainly would have been able to show the PTO its unexpected superiority over prior art compound (b) easily, given compound (b)'s extreme toxicity.

in stark relief, Mylan would have vehemently complained if Takeda had presented to the PTO any toxicity or efficacy numbers other than those in Reports A-15-13 and A-15-34.

Many of the arguments pressed by Mylan (and Alphapharm) at trial flow from a convoluted theory of a conspiracy by Takeda to obtain patent protection for the 6-ethyl.[106] The 6-ethyl is a homolog of compound (b), which is a prior art compound. This theory suffers from several flaws, including most prominently the fact that when Fujita's department applied internally within Takeda to begin the process of applying for the patent that became the '777 Patent, it sought patent protection for the pioglitazone molecule alone and no other compound. In addition, of course, Takeda has never developed a 6-ethyl compound.

In sum, Mylan has failed to carry its burden of showing either a material misstatement or omission. It has also failed to present any evidence of intent to deceive the PTO.

106. The '777 Patent claims include not just the pioglitazone molecule, but also each of the ethyls on the 2-pyridine moiety. The ethyl in the sixth position is referred to as the 6-ethyl.

Conclusion

Each defendant having failed to carry its burden at trial, the challenges to the '777 Patent by Alphapharm on the ground of obviousness and by Mylan on the ground of inequitable conduct are denied. Takeda shall submit a proposed judgment.

SO ORDERED.

APPENDIX C — FINAL JUDGMENT OF THE UNITED STATES DISTRICT COURT FOR THE SOUTHERN DISTRICT OF NEW YORK FILED MARCH 13, 2006

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

Civil Action No.
03 CV 8250 (DLC)

Takeda Chemical Industries, Ltd., and Takeda Pharmaceuticals North America, Inc.,

Plaintiffs,

v.

Ranbaxy Laboratories, Ltd., and Ranbaxy Pharmaceuticals, Inc.

Defendants.

Civil Action No.
03 CV 8253 (DLC)

Takeda Chemical Industries, Ltd., and Takeda Pharmaceuticals North America, Inc.,

Plaintiffs,

v.

Appendix C

Mylan Laboratories, Inc.,
Mylan Pharmaceuticals, Inc., and
UDL Laboratories, Inc.,

Defendants.

Civil Action No.
03 CV 8254 (DLC)

Takeda Chemical Industries, Ltd., and
Takeda Pharmaceuticals North America, Inc.,

Plaintiffs,

v.

Watson Pharmaceuticals, Inc.,
Watson Laboratories, Inc., Watson Pharma, Inc. and
Danbury Pharmacal, Inc.

Defendants.

Civil Action No.
04 CV 1966 (DLC)

Takeda Chemical Industries, Ltd., and
Takeda Pharmaceuticals North America, Inc.,

Plaintiffs,

v.

Alphapharm Pty. Ltd., and Genpharm, Inc.,

Defendants.

Appendix C

FINAL JUDGMENT

This matter having come on for trial on the merits before the undersigned Hon. Denise Cote (without a jury), and having been tried to conclusion between January 17, 2006 and January 30, 2006, and upon all of the prior pleadings and proceedings herein, and upon and in accordance with the Court's Opinion and Order dated February 21, 2006, it is hereby ORDERED, ADJUDGED and DECREED as follows:

1. Defendants Alphapharm Pty. Ltd. and Genpharm, Inc. (collectively "Alphapharm") have failed to meet their burden of proving that U.S. Patent No. 4,687,777 (" '777 Patent") is invalid. The '777 Patent remains valid. All affirmative defenses and counterclaims asserted by Alpharpharm with respect to the '777 Patent are hereby dismissed on the merits and with prejudice.

2. Defendants Mylan Laboratories, Inc., Mylan Pharmaceuticals, Inc. and UDL Laboratories, Inc. (collectively "Mylan") have failed to meet their burden of proving that the '777 Patent is unenforceable. The '777 Patent remains enforceable. All affirmative defenses and counterclaims asserted by Mylan with respect to the '777 Patent are hereby dismissed on the merits and with prejudice.

3. Alphapharm infringed claims 1, 2 and 5 of the '777 Patent by filing Abbreviated New Drug Application ("ANDA") No. 76-799 with the Food and Drug Administration ("FDA") including a certification under

505(j)(2(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355). Alphapharm would further infringe claims 1, 2 and 5 of the '777 Patent by making, using, offering to sell or selling within the United States or by importing into the United States pioglitazone hydrochloride tablets as described in their ANDA.

4. Mylan infringed claims 1, 2 and 5 of the '777 Patent by filing ANDA No. 76-801 with the FDA including a certification under 505(j)(2(A)(vii)(IV) of the Federal Food, Drug and Cosmetic Act (21 U.S.C. § 355). Mylan would further infringe claims 1, 2 and 5 of the '777 Patent by making, using, offering to sell or selling within the United States or by importing into the United States pioglitazone hydrochloride tablets as described in their ANDA.

5. Defendants Ranbaxy Laboratories, Ltd. and Ranbaxy Pharmaceuticals, Inc. (collectively "Ranbaxy") filed ANDA No. 76-800 with the FDA. Ranbaxy did not challenge the validity or enforceability of the '777 Patent in their ANDA or in this action. Ranbaxy would infringe claims 1, 2 and 5 of the '777 Patent by making, using, offering to sell or selling within the United States or by importing into the United States pioglitazone hydrochloride tablets as described in their ANDA.

6. Defendants Watson Pharmaceuticals, Inc., Watson Laboratories, Inc., Watson Pharma., Inc. and Danbury Pharmacal, Inc. (collectively "Watson") filed ANDA No. 76-798 with the FDA. Watson did not

challenge the validity or enforceability of the '777 Patent in their ANDA or in this action. Watson would infringe claims 1, 2 and 5 of the '777 Patent by making, using, offering to sell or selling within the United States or by importing into the United States pioglitazone hydrochloride tablets as described in their ANDA.

7. Alphapharm, Mylan, their officers, agents and employees, and all persons acting (directly or indirectly) in privity or concert with them, are permanently enjoined pursuant to 35 U.S.C. § 271(e)(4)(B) from making, using, offering to sell or selling within the United States and from importing into the United States pioglitazone hydrochloride tablets as described in ANDA Nos. 76-799 (Alphapharm), and 76-801 (Mylan), until the expiration date of '777 Patent, as that date may be extended pursuant to law.

8. Pursuant to 35 U.S.C. § 271(e)(4)(A), the effective date of any approval of ANDA Nos. 76-799 (Alphapharm), 76-801 (Mylan), 76-800 (Ranbaxy) and 76-798 (Watson), or amendments thereof, shall be a date which is not earlier than the expiration date of the '777 Patent, January 17, 2011, as that date may be extended pursuant to law.

9. Plaintiffs Takeda Pharmaceutical Company, Ltd. (formerly Takeda Chemical Industries, Ltd.) and Takeda Pharmaceuticals North America, Inc. (collectively "Takeda") have requested that the Court determine that this case is exceptional with respect to Mylan's and Alphapharm's challenges to the '777 Patent, and have

requested that the Court award their reasonable attorney fees pursuant to 35 U.S.C. § 285. Takeda may file a motion requesting such additional relief by March 31, 2006. Opposition is due April 21. Takeda's reply is due May 5, 2006, on which day Takeda shall supply two courtesy copies of all motion papers to Chambers.

10. There being no just reason for delay, pursuant to Rule 54(b), Fed. R. Civ. P., the Clerk of Court shall enter final judgment for Takeda pursuant to paragraphs 1 through 8.

SO ORDERED.

Dated: New York, New York
March __, 2006

DENISE COTE
United States District Judge

s/ Denise Cote
March 10, 2006

APPENDIX D — JUDGMENT OF THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT DATED JUNE 28, 2007

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

06-1329

TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.,

Plaintiffs-Appellees,

v.

ALPHAPHARM PTY., LTD. and GENPHARM, INC.,

Defendants-Appellants.

JUDGMENT

ON APPEAL from the UNITED STATES DISTRICT COURT SOUTHERN DISTRICT OF NEW YORK

in CASE NO(S) 04-CV-1066

This CAUSE having been heard and considered, it is

ORDER and ADJUDGED.

AFFIRMED

ENTERED BY ORDER OF THE COURT

s/ Jan Horbaly
Jan Horbaly, Clerk

DATED JUNE 28, 2007

APPENDIX E — ORDER OF THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT DENYING PETITION FOR REHEARING EN BANC FILED SEPTEMBER 27, 2007

UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

2006-1329
(DCT - 04-CV-1966)

TAKEDA CHEMICAL

V

ALPHAPHARM PTY

A petition for rehearing en banc having been filed by the Appellants and a response thereto having been invited by the court and filed by the Appellees and the matter having first been referred as a petition for rehearing to the panel that heard the appeal, and thereafter the petition for rehearing en banc and response having been referred to the circuit judges who are in regular active service,

UPON CONSIDERATION THEREOF, it is

ORDERED that the petition for rehearing be, and the same hereby is, DENIED and it is further

ORDERED that the petition for rehearing en banc be, and the same hereby is, DENIED.

Appendix E

The mandate of the court will issue on October 4, 2007.

Circuit Judge Schall did not participate in the vote.

FOR THE COURT,

s/ Jan Horbaly
Jan Horbaly
Clerk

Dated: 09/27/2007

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No. 07-838

FILED
FEB 27 2008
OFFICE OF THE CLERK
SUPREME COURT, U.S.

IN THE

Supreme Court of the United States

ALPHAPHARM PTY., LTD. and GENPHARM, INC.,

Petitioners,

v.

TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BRIEF IN OPPOSITION

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QUESTION PRESENTED

Putting aside the numerous assertions about the Federal Circuit decision on its Question Presented pages, the Petition presents the sole question: whether the Federal Circuit decision materially conflicts with this Court's decision in the *KSR* case, which the Federal Circuit fully addressed and applied to the quite different facts of this case.

CORPORATE DISCLOSURE STATEMENT

Respondent, Takeda Chemical Industries, Ltd. (now known as Takeda Pharmaceutical Company Limited) does not have a parent corporation and there is no publicly held company that owns 10% or more of its stock. Respondent, Takeda Pharmaceuticals North America, Inc., is a wholly owned subsidiary of Takeda Chemical Industries, Ltd.

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35 U.S.C. § 282 ..... 1, 2, 15

STATUTORY PROVISIONS

In addition to 35 U.S.C. § 103, this case is controlled by 35 U.S.C. § 282:

> A patent shall be presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims. . . . The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity.

INTRODUCTION

Alphapharm's Petition contends that the Federal Circuit imposed a "new and onerous" requirement to establish a prima facie case of obviousness and rigidly applied the so-called "teaching, suggestion, motivation" ("TSM") test in a manner inconsistent with this Court's decision in *KSR International Co. v. Teleflex, Inc.*, 127 S. Ct. 1727 (2007). In reality, however, the Federal Circuit neither applied a rigid TSM test nor imposed any new threshold requirement; nor did it otherwise apply a standard inconsistent with *KSR*. Rather, the Federal Circuit correctly applied this Court's precedent to the particularized facts of this case to affirm the district court's extensive findings of fact under *Graham v. John Deere Co.*, 383 U.S. 1 (1966). Utilizing the *Graham* factors is precisely the approach advocated in *KSR*: the "framework for applying the statutory language of § 103," explicitly set out in *Graham*, "continue[s] to define the inquiry that controls." 127 S. Ct. at 1734.

The Petition's assertion that the Federal Circuit "rigidly" applied a TSM approach is a makeweight, attempting to grab on to *KSR*. The assertion mischaracterizes the Federal Circuit decision. The Federal Circuit evaluated and affirmed a fact-specific analysis of all the evidence – not just prior-art documents, but the testimony of experts and of Alphapharm's own representatives – as to what would have been obvious. That all-the-evidence approach, expressly following the *Graham* analysis, is just what *KSR* commends. 127 S. Ct. at 1734.

Alphapharm's real complaint is that the Federal Circuit did not give it the benefit of a *presumption* of obviousness in light of a structurally similar prior-art compound. Pet. i, 2, 12 (asserting a *rule* presuming "that structurally similar compounds . . . are prima facie obvious"). That position, however, would improperly replace the full-context *Graham-KSR* approach with a new rigid rule of obviousness, specific only to the chemical arts. Noticeably, the Petition never cites a decision of this Court for that asserted presumption. That is hardly surprising, for that approach is not just contrary to 35 U.S.C. § 282, but to the central lesson of *KSR* itself – that rigid and mandatory rules are to be avoided in favor of fact-specific inquiries into what skilled artisans would or would not have done or seen. The gravamen of the Petition thus would turn the lesson of *KSR* on its head.

Accordingly, no legal question warranting review is presented. Indeed, after *KSR* was decided, this Court denied certiorari from a quite similar decision rejecting

obviousness, as Alphapharm acknowledges. *See* Pet. 22-23 (discussing *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369 (Fed. Cir. 2006), *cert. denied*, 128 S. Ct. 146, 128 S. Ct. 288 (2007)). Not only did the two Petitions from that decision make arguments nearly identical to what Alphapharm now advances,[1] but the Respondents in *Eli Lilly* relied extensively on the Federal Circuit's decision in the present case to explain how the *Eli Lilly* decision (rendered before *KSR* was decided) was consistent with *KSR*. *See* Brief for Respondents, *Teva Pharms. USA, Inc. v. Eli Lilly & Co.*, 128 S. Ct. 146, 128 S. Ct. 288 (2007) (Nos. 06-1642, 06-1723), 2007 WL 2212737, at *16-17. Thus, this Court denied certiorari outright, rather than remand for reconsideration in light of *KSR*, even though the Federal Circuit in *Eli Lilly* had not had a chance to consider *KSR*. Here, the Federal Circuit carefully applied *KSR*, and the Petition should likewise be denied.

Ultimately, rather than raising any question of "legal significance," Alphapharm bases its Petition on an attempt to relitigate the facts it alleged, but failed to prove, below. That is not a "compelling reason" for review on a writ of certiorari. *See* SUP. CT. R. 10.

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1. *See* Brief for Petitioners-Appellants, *Teva Pharms. USA, Inc. v. Eli Lilly & Co.*, 128 S. Ct. 146 (2007) (No. 06-1642), 2007 WL 1685850, at *13-16 (challenging purported imposition of requirements to show: "motivation for one of ordinary skill in the art to" (1) "select a prior art compound as a 'lead compound,'" and (2) "modify [that] prior art compound to arrive at the patented compound."); Brief for Petitioner-Appellant, *Dr. Reddy's Labs., Ltd. v. Eli Lilly & Co.*, 128 S. Ct. 288 (2007) (No. 06-1723), 2007 WL 1850384 (same).

In any event, certiorari should be denied for the additional reason that the decision below independently rests on another ground – unexpected results that rebutted any prima facie case of obviousness, had one existed. Alphapharm never addresses or asserts error in the district court's finding that "[e]ven if Alphapharm had been able to show a prima facie case of obviousness, there is compelling and conclusive evidence that pioglitazone's non-toxicity was unexpected" (A96, A127-29),[2] or in the Federal Circuit's affirmation that the district court's "characterization of pioglitazone's unexpected properties is not clearly erroneous," and that "[c]onsequently, Takeda rebutted any presumed expectation that compound b and pioglitazone would share similar properties." A24. Alphapharm has thus failed to raise any question that could justify overturning the ultimate finding of the district court that the patent at issue is valid, or the Federal Circuit's affirmance of that finding.

STATEMENT OF THE CASE

I. Factual Background

A. The '777 Patent

Takeda owns the patent-in-suit, U.S. Patent No. 4,687,777 ("'777 patent"), which issued on August 18, 1987 (RA814-20) and will expire on January 17, 2011 (A74-75). The '777 patent shows that pioglitazone is exceptional, out of a class of hundreds of millions of

2. "A__" refers to the petition appendix in this Court. "RA__" refers to the Unified Joint Appendix in the Federal Circuit No. 06-1329, and "SA__" refers to Alphapharm's "Supplementary Appendix" filed with its Petition in this Court.

compounds, because it is both effective *and safe* for treatment of Type 2 Diabetes. A33; A68; RA814-20; *see* A12-26. Prior to the discovery of pioglitazone, other prior art compounds in this class that appeared effective were toxic. RA816(col. 1, ll. 18-40); A96; *see* A23-24. Others were safe, but ineffective. RA818(col. 1, ll. 18-40). Even Alphapharm's Rule 30(b)(6) designee, who is himself a medicinal chemist and the director of Alphapharm's Intellectual Property strategy, agreed that the data in the '777 patent established that pioglitazone is "clearly superior" to the prior art. A37; A127; *see* RA2186(17:14)-2187(19:7); *see also* RA2241(235:25-236:4); RA3177 (1238:16-23).

In July 1999, after extensive testing and clinical trials, the FDA approved pioglitazone (ACTOS®) for treatment of Type 2 Diabetes, finding it safe and effective. ACTOS® was such an important advance in medicine that it has been hugely successful, attaining annual sales in the United States of over $1.7 billion in 2003 and over $2 billion in 2004. A3; A129-131; RA4816; *see* A41. Other than pioglitazone, the FDA has only ever approved two other thiazolidinediones ("TZDs"). Rezulin®, the first FDA-approved TZD, was withdrawn due to lethal liver toxicity. A40-41; RA4824-27. Avandia® is the only other FDA-approved TZD on the market today, but studies have shown that ACTOS® is highly superior to Avandia® in its triglyceride lowering, its effects on cholesterol, its tendency to *improve* cardiovascular outcomes, and its multiple beneficial effects for atherosclerosis. A40-41; *see, e.g.*, RA1059-1063. Indeed, Alphapharm chose to pursue ACTOS® over Avandia® because of its "selective advantage." RA6644.

B. Discovery of Pioglitazone

In the mid 1970s, Takeda researchers discovered that certain TZD derivatives lowered blood glucose in diabetic mice. A2-3; A41-44; RA1076(¶25). TZDs, now known as "insulin sensitizers," appeared to have the unique potential to overcome a primary cause of Type 2 Diabetes, namely, resistance to the action of insulin. Over the next decade, Takeda studied over 2,000 separate compounds, including approximately 1,000 TZDs. A33; A41-66; RA1076-78.

Prior to the discovery of pioglitazone, many in the scientific community believed that research into "insulin sensitizers" was the wrong direction. A56; RA1614-15(¶21). Nevertheless, Takeda and its researchers forged ahead. Extensive studies on TZDs led to the synthesis of ciglitazone in February 1978, as well as many other TZDs. A44-54. As Takeda's development work progressed, however, the development team observed that ciglitazone exhibited significant toxicities, and that it was not sufficiently effective to be a successful antidiabetic. A53-54.

During its evaluation of ciglitazone, Takeda continued to search for compounds that were both safer and more effective. A53-56. Pioglitazone, internally designated AD-4833, was first synthesized on September 7, 1982. A54. Several years of additional work showed that pioglitazone was the only efficacious TZD of the hundreds tested that had no statistically significant toxicity to the heart, liver or erythrocytes (red blood cells) in standard two-week toxicity screening tests, and showed no toxicity in tests for cataract formation

(a toxicity that contributed to the discontinuation of ciglitazone's clinical trials). A23-24; A54-66; RA4638-55; RA4659-83. Takeda was excited to find that "the data of all preliminary toxicological studies so far obtained were clear" for pioglitazone. RA4692; *see* A62-66.

C. Prosecution History of The '777 Patent

The '777 patent "is directed to 'compounds which can be practically used as antidiabetic agents having a broad safety margin between pharmacological effect and toxicity or unfavorable side reactions.'" A3 (quoting RA816(col. 1, ll. 34-37)). The patent disclosure included experimental data from Takeda Official Reports A-15-34 and A-15-13, the same data Takeda had relied on in selecting pioglitazone for development. A23; A59-70; RA893-924; RA4638-55; RA4659-83.

The applicants additionally filed an Information Disclosure Statement ("IDS") that directed the Examiner's attention to several pertinent prior art references (discussed further below). The IDS expressly depicted the chemical structure of the closest prior art, designated in the '777 patent as compound b. RA856. The Examiner considered compound b, but did not reject the claims for obviousness over that compound or others. The Examiner did ask for clarification of the specification. A73-74; RA870-73. After Takeda filed a responsive Amendment and Declaration (RA876-85; RA886-92), the application was allowed, and the '777 patent issued (RA774; RA814).

In this action, Takeda relied on three claims: claim 1 covers a small group of four ethylated 2-pyridyl thiazolidinedione compounds and their pharmacologically acceptable salts; claim 2 is specifically directed to one of those compounds, pioglitazone, and its pharmacologically acceptable salts; and claim 5 covers a pharmaceutical whose active ingredient is one of the group of four compounds of claim 1 or a pharmacologically acceptable salt thereof. A3-5; A67-68; RA820(col. 10, ll. 28-65).

II. The District Court Decision

Four generic drug manufacturers, including Alphapharm and Mylan, filed Abbreviated New Drug Applications ("ANDAs") for pioglitazone. A80-81. Only Alphapharm and Mylan attacked the '777 patent as invalid for obviousness, although on different and contradictory grounds. Mylan later abandoned its obviousness claim. A81-86.

The district court took thousands of pages of direct testimony of over two dozen fact and expert witnesses by declaration and deposition transcripts, and it received thousands more pages of supporting exhibits. The court presided over eight trial days of live cross-examination, giving it the opportunity to extensively observe and examine the parties' witnesses. *See generally* A33-37; RA2267-3406. After considering all the evidence, the district court issued a 124-page opinion rejecting Alphapharm's challenge, holding that Alphapharm "failed to make even a rudimentary showing that the invention was obvious. . . ." A33.

Although Alphapharm attempts to portray the district court's "view of the law" as inconsistent with this Court's decision in *KSR*, Alphapharm wholly ignores the district court's fundamental statement and analysis of the law under *Graham*:

> The talismanic statement of the obviousness inquiry appears in *Graham*, which identifies four factual underpinnings to a determination of obviousness: (1) the scope and content of the prior art, (2) the level of ordinary skill in the art, (3) the differences between the prior art and the claimed invention, and (4) objective indicia of non-obviousness.

A91. That statement of the relevant inquiry, and the district court's analysis of the facts under it, are entirely consistent with this Court's unequivocal reaffirmation that *Graham*, "continue[s] to define the inquiry that controls." *KSR*, 127 S. Ct. at 1734.

III. The Federal Circuit's Affirmance

The Federal Circuit carefully reviewed the district court's findings under the *Graham* factors as well as the underlying record, including all of the prior art relied on by Alphapharm. The Federal Circuit held that:

> Alphapharm's challenges fail to identify grounds for reversible error. The [district] court properly considered the teachings of the prior art and made credibility determinations regarding the witnesses at trial.... Because the court's

> conclusions are not clearly erroneous and are supported by the record evidence, we find no basis to disturb them.

A25. Among the district court's findings affirmed by the Federal Circuit was the determination that "the closest prior art compound (compound b, the six-methyl) exhibited negative properties that would have directed one of ordinary skill away from that compound" – a determination of fact. A18; *see In re Harris*, 409 F.3d 1339, 1341 (Fed. Cir. 2005), *cert. denied*, 546 U.S. 1090 (2006); *In re Berg*, 320 F.3d 1310, 1312 (Fed. Cir. 2003) ("What the prior art teaches and whether it teaches away from the claimed invention are questions of fact."); *see also Graham*, 383 U.S. at 17-18 (discussing "basic factual inquiries.").

Alphapharm petitioned the Federal Circuit for panel rehearing and rehearing *en banc*, asserting fact-based arguments which are nearly identical to those advanced to this Court. The Federal Circuit rejected that petition. A170-71.

REASONS FOR DENYING THE PETITION

The Federal Circuit's decision does not conflict with the decision of any other court of appeals or, contrary to petitioners' claim, with the decision of this Court in *KSR*. Although Alphapharm cloaks its attempt to relitigate the facts in the guise of a "legal question" concerning the standard for obviousness, no such question exists. Both the district court and the Federal Circuit applied the correct legal standard, set forth in *Graham* and reaffirmed by this Court in *KSR*. *See KSR*, 127 S. Ct. at 1734. *Graham* expressly recognized that "[m]anifestly, the validity of [the patent in suit] turns on the facts," 383 U.S. at 5, and thus requires the fact-finder to consider four factual inquiries: "1) 'the scope and content of the prior art'; 2) the 'differences between the prior art and the claims'; 3) 'the level of ordinary skill in the pertinent art'; and 4) objective evidence of nonobviousness." A9-10 (quoting *KSR*, 127 S. Ct. at 1734 (quoting *Graham*, 383 U.S. at 17-18)). Here, "[i]n a thorough and well-reasoned opinion, albeit rendered before *KSR* was decided by the Supreme Court, the district court made extensive findings of fact and conclusions of law as to the four *Graham* factors." A10. The Federal Circuit then scrupulously examined the issues in light of and in accordance with *KSR* itself. *See generally* A1-30.

Alphapharm's Petition ultimately asks this Court to disregard the district court's fact-findings, as affirmed, and to find that Alphapharm "demonstrated" an entirely different set of "facts" at trial. *See, e.g.*, Pet. i, 3, 17, 20. Such a request is not an appropriate ground for certiorari. This Court has refused to second-guess

concurrent factual findings made by two courts below. *See, e.g., Graver Tank & Mfg. Co. v. Linde Air Prods. Co.*, 336 U.S. 271, 275 (1949), *aff'd on reh'g*, 339 U.S. 605 (1950).

In any event, the district court, as affirmed by the Federal Circuit, had ample grounds to reject Alphapharm's version of the facts. The vast majority of Alphapharm's "facts" were supported only by the testimony of Alphapharm's expert, Dr. Mosberg, whose opinions were explicitly rejected by the district court. *See* SA93-121. The court found that, on cross-examination, Dr. Mosberg "directly contradict[ed] his direct testimony" (A109), "directly contradict[ed] Alphapharm's proposed findings of fact" (A109 n.54), presented a "recently invented analysis" which was "not supported by any intellectually rigorous analysis" (A109), and testified with "some creativity but little persuasion." A110. The court found Takeda's experts "superbly qualified" (A98), "preeminent" (A98 n.39), and "far more credible" than Dr. Mosberg (A118). That evidence, along with the other testimony and documents supporting Takeda's case, fully supported the rejection of Alphapharm's assertion of a prima facie case of obviousness.

The record also supported the finding of unexpected results that would overcome any prima facie case of obviousness – a finding that independently supports the judgment and is not even challenged by Alphapharm.

I. The Federal Circuit's Decision Is Consistent with *KSR*

Alphapharm argues that the Federal Circuit "rigidly" applied the "TSM" test. Pet. 2-3, 13-16. The Federal Circuit did no such thing. It reviewed the district court's findings under *Graham* and affirmed that "the court did not err in holding that Alphapharm failed to establish a prima facie case of obviousness." A20. In reaching this determination, the Federal Circuit analyzed its precedent relevant to prima facie obviousness for chemical compounds, and the impact of *KSR* thereon, and observed that:

> [I]n cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.

A12. That reference to "some reason" is not a "rigid" application of TSM. And it is entirely consistent with *KSR*, which "acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine elements in the way the new claimed invention does in an obviousness determination.'" *Id.* (quoting 127 S. Ct. at 1741). Alphapharm's contention that the Federal Circuit "required particular explicit motivation" is unsupported by the opinion's text. Pet. 12. *Compare* Pet. 3, 12, 24 *with* A1-30. As *KSR* pointed out, "[t]here is no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis," noting that TSM may provide a "helpful insight." 127 S. Ct. at 1741.

Even Alphapharm concedes that a patent challenger must point to "an apparent reason to combine the known elements in the fashion claimed." Pet. 16 (citing *KSR*, 127 S. Ct. at 1741). Alphapharm attempted, but failed, to meet that burden by claiming as *fact* that the prior art would have led one of ordinary skill in the art to select compound b as a "lead compound," and to modify it in particular ways.[3] A12-13. But, as the district court found, and the Federal Circuit confirmed: "Alphapharm failed to make that showing here." A12.

To avoid this failure of proof, and to manufacture some claimed error, Alphapharm proposes to establish a conclusive presumption of obviousness, urging this Court to hold the '777 patent claims "obvious as a matter of law." Pet. 26; *see also* Pet. 12; *id.* at i (arguing that compounds "so closely related in structure to the closest prior art . . . [are] presumed obvious under patent law."). Alphapharm's overreaching is not supported by *KSR*. In fact, *KSR* disapproved of "rigid and mandatory formulas." *Id.* at 1741. By seeking to rely on an (improper) presumption, and by ignoring relevant facts (such as toxicity, unexpected results, or secondary indicia of nonobviousness), it is Alphapharm which is asserting a "rigid and mandatory" rule, not the Federal Circuit.

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3. Alphapharm faults the Federal Circuit for "deciding the appeal as it has been argued [by Alphapharm]," asserting that "it is the province of the Federal Circuit to decide the case as the law requires." Pet. 24. That is simply another attempt by Alphapharm to disguise its failures of proof as implicating some non-existent legal issue. In any event, Alphapharm's fault-finding is necessarily at odds with the positions it advocated below. "Ordinarily, doctrines of estoppel, waiver, invited error, or the like would prohibit a party from asserting as 'error' a position that it had advocated [below]." *Key Pharms. v. Hercon Labs. Corp.*, 161 F.3d 709, 715 (Fed. Cir. 1999).

Moreover, in *KSR*, this Court expressly reaffirmed that: "[b]y direction of 35 U.S.C. § 282, an issued patent is presumed valid." 127 S. Ct. at 1737.

While a prima facie case of obviousness of an issued patent *may* be based on structural similarity between the claimed compound and the prior art, that prima facie case is never presumed – it must be *proved* by the challenger. The Federal Circuit correctly stated this rule as follows:

> Our case law concerning prima facie obviousness of structurally similar compounds is well-established. We have held that "structural similarity between claimed and prior art subject matter, proved by combining references *or otherwise*, where the prior art gives reason or motivation to make the claimed compositions, creates a prima facie case of obviousness." [In re] *Dillon*, 919 F.2d [688], 692 [(Fed. Cir 1990), *cert. denied*, 500 U.S. 904 (1991)]. In addition to structural similarity between the compounds, a prima facie case of obviousness also requires a showing of "adequate support in the prior art" for the change in structure. *In re Grabiak*, 769 F.2d 729, 731-32 (Fed. Cir. 1895).

A10-11 (emphasis added); *see Eli Lilly*, 471 F.3d at 1377-78. As the Federal Circuit recognized, this standard is entirely consistent with the Court's decision in *KSR*, which requires proof of facts showing "an apparent

reason to combine the known elements in the fashion claimed." *KSR*, 127 S. Ct. at 1740-41; A12.[4]

Nor was the Federal Circuit's decision inconsistent with *KSR*'s statement that "[w]hat matters is the objective reach of the claim." 127 S. Ct. at 1742. This Court's point was simply that it is a mistake to limit an obviousness analysis to asking what problem the particular inventors were working on, rather than "any need or problem known in the field of endeavor at the time of invention," to determine whether "the claim extends to what is obvious." *Id.* Nothing whatsoever in the Federal Circuit decision here makes that mistake. To the contrary, that court, like the district court, clearly focused on the perspective of the entire field, and considered all the pertinent prior art as a whole without the sorts of limitations which this Court found problematic in *KSR*. Both courts engaged in an intensive

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4. Alphapharm (Pet. 12) quotes *In re Grabiak*, 769 F.2d at 731, but even the quote does not support Alphapharm's assertion that structural similarity always triggers a presumption of obviousness: it says that "when chemical compounds have 'very close' structural similarities and similar utilities, without more, a *prima facie* case *may be* made." (emphasis added). Indeed, *Grabiak* explained that "generalization should be avoided insofar as specific chemical structures are alleged to be *prima facie* obvious one from the other," *id.* at 731, and held that the PTO failed to meet its burden of "perfecting" a prima facie case because its "argument is lacking in a critical element: *adequate support in the prior art*." *Id.* at 731-33 (emphases added). Other lower-court decisions cited by Alphapharm confirm that even in proceedings before the PTO (*i.e.*, before a patent issues and so before the presumption of *validity* in § 282 applies), a prima facie case must be "proved." *In re Dillon*, 919 F.2d at 692; *In re Mayne*, 104 F.3d 1339, 1341-42 (Fed. Cir. 1997).

factual analysis of the teachings of the prior art as a whole, including U.S. Patents Nos. 4,438,141 ("'141 patent"), 4,461,902 ("'902 patent"), and 4,340,605 ("'605 patent"),[5] in addition to Sohda II and the U.S. Patents Nos. 4,287,200 ("'200 patent") and 4,444,779 ("'779 patent"). *See, e.g.*, A14-16; A114.

Alphapharm does not suggest that some art was excluded because it was from a different field. Alphapharm accuses the Federal Circuit of "fail[ing] to perform an analysis based on the objective reach of the claim," but as support for that bald assertion, Alphapharm contends that the Federal Circuit required proof that a skilled person would select compound b as a lead compound. Pet. 14-16. Simply put, Alphapharm's argument has nothing to do with the "objective reach of the claim" language in *KSR*.

Moreover, Alphapharm's argument wrongly reads this Court's reference to the "objective reach of the claim" as supporting its impermissible "hindsight" obviousness analysis. As discussed below, Alphapharm

5. Prior to the '777 filing date, several additional patents issued to Takeda covering different classes of TZDs (*i.e.*, compounds with significantly different structures than those at issue in this case). A47-48; A53; *see* A15-16; A27; *see also* RA3155(1205:6)-RA3157(1208:3). The '141 patent, a divisional of the '200 patent, issued March 20, 1984. RA3437-48. It covered TZD compounds with a thienyl, furyl, piperidino, morphylino, or pyrrolidino moiety. *Id.* The '605 patent, also a divisional of the '200 patent, issued July 20, 1982. RA3408-18. It covered TZD compounds with a pyridyl or thiazolyl moiety. *Id.* The '902 patent, issued July 24, 1984, was not a divisional of the '200 patent. RA3427-36. It covered TZD compounds with a substituted cyclohexyl moiety. *Id.*

admitted that its obviousness analysis began with compound b because it was the closest compound structurally to pioglitazone – the patented invention. A108; RA2224(169:17-18). Yet this Court's jurisprudence consistently warns against just such backward-looking analysis. *KSR*, 127 S. Ct. 1742 ("A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." (noting that *Graham*, 383 U.S. at 36 "warn[s] against a 'temptation to read into the prior art the teachings of the invention in issue' and instruct[s] courts to 'guard against slipping into the use of hindsight.'") (internal citations omitted)). *KSR's* reference to the "objective reach of the claim" did not alter that prohibition.

Finally, neither the Federal Circuit nor the district court in this case departed from this Court's carefully qualified statement that "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp." *KSR*, 127 S. Ct. at 1732. The Federal Circuit expressly quoted that principle and simply found, as the district court had, that its factual preconditions are not met here:

> Rather than identify predictable solutions for antidiabetic treatment, the prior art disclosed a broad selection of compounds any one of which could have been selected as a lead compound for further investigation. Significantly, the closest prior art compound (compound b, the 6-methyl) exhibited negative

> properties that would have directed one of ordinary skill in the art away from that compound.

A18; *see* A112-13. There is accordingly no legal issue warranting review.

II. The Courts Below Correctly Held, on the Facts, That Alphapharm Failed to Prove a Prima Facie Case of Obviousness

On the record, the lower courts' rejection of a prima facie case of obviousness in light of compound b (the closest prior-art compound) is correct.

A. Alphapharm presented its case based on the assertion that compound b would have been chosen by those of skill in the art at the time because the "prior art repeatedly quantified [it] as the most potent antidiabetic." Pet. 23; *see id.* at 17. The district court, affirmed by the Federal Circuit, properly rejected that assertion. Compound b was one of many possibilities; the overall prior art did not recommend it over myriad other directions, but in fact recommended structurally different compounds. A14-16 (citing A102-04, A114). Indeed the prior art as a whole taught away from that particular compound. *Id.*

The record evidence supports the district court's rejection of Alphapharm's factual contention. First the Sohda II reference gave *seven* structurally-diverse compounds (compounds 10, 12, 15, 18, 58, 73, and 99) "the highest combined efficacy score, which was a rating of 7." A106; RA1001-21; *accord* RA3144(1189:15)-

RA3146(192:17). Sohda II also identified problems with toxicity or significant adverse health effects for each and every one of those compounds (including compound b) – except for compound 99, a compound that is structurally very different from compound b. A16 (citing A106 n.51). The conclusion drawn in Sohda II was to recommend three *other* compounds entirely, based on their combination of efficacy and toxicity. As the Federal Circuit summarized:

> Significantly, Sohda II identified three specific compounds that were deemed most favorable in terms of toxicity and activity. Notably, compound b was not identified as one of the three most favorable compounds. On the contrary, compound b, was singled out as causing "considerable increases in body weight and brown fat weight."

A15; *see* A48-52; A122-23; RA1010.

Contrary to Alphapharm's assertions, neither the Fujita Declaration that Takeda submitted to the PTO (RA693-98) nor the Amendment accompanying it (RA688-92) – filed in the prosecution that led to the '200 patent – purported to identify "the best nine compounds to overcome certain prior art" (Pet. 5) or "promoted the potent antidiabetic activity of compound b" (Pet. 23). The Amendment and Fujita Declaration made the limited claim that the group of listed compounds as a whole was "far superior to [certain other] compounds which are outside the scope of the present invention [*i.e.*, compounds (i) – (iv)]. . . ." RA691. Alphapharm's own expert admitted, after studying the '200 file history,

that he "did not have an informed opinion whether a person of ordinary skill in the art with only the Fujita 1980 declaration would have made decisions about what compound to designate their lead or to guide their research." RA3136(1177:21)-RA3137(1178:21). There was simply:

> nothing in the '200 patent, or in its file history, to suggest to one of ordinary skill in the art that those nine compounds, out of hundreds of millions of compounds covered by the patent application, were the best performing compounds as antidiabetics, and hence targets for modification to seek improved properties.

A14 (citing A102-04).

When Alphapharm filed its ANDA-required "Detailed Statement," it failed to articulate any reason why one skilled in the art would select compound b (referred to as compound 58 in Sohda II) as a "lead." A102 n.47; A5732-44. And in a candid admission of impermissible hindsight, Alphapharm's first Rule 30(b)(6) witness on this topic, Dr. Rosenberg, conceded that "he only chose compound (b) from Sohda II 'because it was similar to pioglitazone.'" A108; RA2224(169:17-18). He further "admitted that there was nothing in the [Sohda II] article that would recommend that a person of ordinary skill in the art choose compound b over other compounds in the article that had the same efficacy rating." A16-17; *see* A108; RA2225(172:10-20).

Alphapharm's next Rule 30(b)(6) designee, Barry Spencer, came up with a different answer, testifying that

the person of ordinary skill would actually have chosen to investigate three separate but co-equal compounds in Sohda II, namely compounds 47 and 49, which are not pyridyl compounds, and 58 (compound b). A17; A6082(58:14-59:11). Alphapharm's trial expert, Dr. Mosberg, acknowledged that a person of ordinary skill in the art would *not* have focused particularly on compound 58, claiming instead that the person of ordinary skill in the art would have engaged in a research program designed to investigate various permutations on *all* of the 2-pyridyl, 3-pyridyl, and 4-pyridyl compounds (although with a higher priority on 2-pyridyl and 3-pyridyl). A114 n.61; RA3144(1189:4-14); A3146(1192:10-14); *see* A114-17. Finally, as the district court specifically noted, Dr. Mosberg contradicted Alphapharm's position when he testified that the statement about compound b contained in the '779 file history[6] would have led the skilled artisan *away* from that

6. The original application for the '200 patent included a large number of claims directed to various embodiments of the general formula. A45-47; *see* A14 n.4. The Examiner issued a restriction requirement, *requiring* Takeda to prosecute claims to different types of TZD compounds in separate divisional patent applications. A14; A45-48; A111. Thus, the original '200 application was divided into four separate applications, which were considered by the PTO serially, and which resulted in four separate patents: the '200 patent (RA596-605), the '605 patent (RA3408-18), the '141 patent (RA3437-3519), and the '779 patent (RA725-813), all of which are substantially identical except for the claims and the introductory numbering. A45-48; A52; A111; RA3541(¶58); RA6855-58(¶¶31-38). On March 15, 1983, Takeda filed the divisional application that issued as the '779 patent. A52; RA751-84. That application *expanded* the group of compounds previously claimed in the '605 patent. A52; A111; *see* RA6857-58(¶37), and claimed a large group of millions of compounds from the original '200 application. A15-16; A25; A52. The '779 patent issued after Takeda agreed to a Terminal Disclaimer making its expiration the same as that of the '605 patent. A52; RA798-99.

compound. A108-09; *see* A109 n.54 and accompanying text; RA3143(1187:16)-3144(1188:25); RA3148(1195:6)-3149 (1197:3).

Alphapharm complains that the district court "turned a deaf ear" to the statement in the '779 file history "that compound b had become 'especially' 'important.'" Pet. 21. That is incorrect. The district court expressly considered that material and the testimony offered by both parties about its import to the skilled artisan. As the Federal Circuit noted:

> Based on the prior art as a whole, however, the [district] court found that a person of ordinary skill in the art would not have selected compound b as a lead compound for antidiabetic treatment. Although the prosecution history of the '779 patent included the statement that characterized compound b as "especially important," ... any suggestion to select compound b was essentially negated by the disclosure of the Sodha II reference. The court reasoned that one of ordinary skill in the art would not have chosen compound b, notwithstanding the statement in the '779 patent prosecution history, "given the more exhaustive and reliable scientific analysis presented by Sodha II, which taught away from compound b, and the evidence from all of the TZD patents that Takeda filed contemporaneously with the '779 [p]atent showing that there were many promising, broad avenues for further research."

A15-16 (quoting A114).

Alphapharm's complaint that the district court "overemphasiz[ed] the side effects of compound b noted in Sohda II" (Pet. 21) is inconsistent with its own expert's testimony that the "Sohda [II] article is the key piece of prior art that the skilled artisan would look to. . . ." RA1834(¶27); *see* A98-99; *accord* RA3164(1219:1)-RA3165(1219:23). The record amply supports the finding that Sohda II "teaches away" from compound b, and the application of "common sense" supports this conclusion. *KSR*, 127 S. Ct. at 1742. Sohda II, itself, states at A1010 that "especially 57 and 58 [compound b] caused considerable increases in body weight and brown fat weight." Mylan's 30(b)(6) designee testified that the skilled artisan "would and should . . . rule . . . out" compounds 57 and 58 [compound b] because they "caus[e] considerable increases in body weight and brown fat weight, which would be on the toxicity side of the equation." RA6462(132:14)–RA6463(134:15). Alphapharm's Rule 30(b)(6) designee admitted that such a compound is "presumably not" desirable. RA2227(180:24-181:13). Alphapharm's own expert, Dr. Mosberg, agreed that "[a] medicinal chemist skilled in the art would probably read the article and accept *Sohda et al.* [sic] claim that increase in brown fat and weight gain were undesirable." RA3128(1165:10)-3129(1167:11); *see* RA3191(1259:7-12) (noting that "it would seem logical" that "weight gain in a diabetic is not a good thing.").

Contrary to Alphapharm's representation, Takeda's witnesses (Drs. Morton, Colca, and Koller) did not "admit" otherwise. *Cf.* Pet. 21-22. Dr. Morton unequivocally stated that "because of data indicating that pyridyl derivatives [compounds 57 and 58] caused such adverse health effects, people involved in or interested in this research, reading Sohda II at the time, myself included, would conclude that

this reference taught away. . . ." RA1615(¶22). Dr. Colca testified that "some people . . . were just so concerned about weight and the fact that Type II diabetics are normally heavy anyway, that we should be focusing on compounds that cause weight loss rather than weight gain, or are at least weight neutral." RA3004(982:24-983:3). Similarly, Dr. Koller testified that "reading the Sohda II text, one would eliminate compounds 57 and 58 . . . as candidates for further research as pharmaceutical compounds for the treatment of Type 2 Diabetes Mellitus at that time." RA3626(¶¶19-20).

The district court's consideration of these facts is entirely in accord with this Court's precedents. "[K]nown disadvantages in old devices which would naturally discourage the search for new inventions may be taken into account in determining obviousness." *U.S. v. Adams*, 383 U.S. 39, 52 (1966).

B. Of course, even had Alphapharm shown that an artisan seeking a medically beneficial result had focused on compound b, there was a second factual element of its case which it also needed to prove, *i.e.*, that making the changes needed to arrive at the patented compounds was a "predictable use of prior art elements according to their established functions." Pet. 16 (quoting *KSR*, 127 S. Ct. at 1740). By its own admissions, this was a necessary "threshold inquiry." *Id.* Yet the record amply demonstrates that Alphapharm failed to meet this fact-bound "threshold." Alphapharm's expert, Dr. Mosberg, admitted that "the biological activities of various substituents were 'unpredictable' based on the disclosure of Sohda II." A21 (citing A124-26); *see* RA5115-19; RA3171(1229:10-18). Dr. Mosberg agreed with Takeda's

"far more credible" (A118) expert, Dr. Danishefsky, and admitted that even where methyl-to-ethyl substitutions are made in Sohda II, the resulting biological activity was highly unpredictable. A19-23; A118-20; RA1169-79(¶¶125-48); *accord* RA3192(1261:1)-RA3195(1265:2); RA3197 (1267:13)-RA3198(1269:17). Moreover, Dr. Mosberg conceded that his espoused process of so-called "routine optimization" (upon which Alphapharm continues to rely, citing SA111-13 throughout §C of its Petition) results in success in "at most 1%" of the time. A117; RA3165(1220:11)-3168(1224:10). Additionally, Alphapharm's Rule 30(b)(6) designee, Dr. Rosenberg, admitted that "a person of ordinary skill in the art would 'look at a host of substituents, such as chlorides, halides and others, not just methyls'" (A20 (citing A118); *see* RA2224(167:7-10)), and would have to undertake an extensive research effort to determine the effect of each change (RA2236(216:15)-RA2238(222:2)). Indeed, Dr. Mosberg admitted that the skilled artisan would not be able to predict: (1) whether any particular structural modification would or would not result in a change in biological properties; (2) if there was any such change, whether the difference would be to toxicity or efficacy, or both; or (3) whether that change would be favorable or unfavorable. RA3170(1227:23)-RA3171(1229:18); *see* A125-26.

Yet in the face its own admissions, Alphapharm falsely states that it "demonstrated the reason to modify at trial." Pet. 17. But its "demonstration" is based only on the testimony of its discredited expert and otherwise unsupported attorney argument, and wholly fails to address the fact that – as its witnesses repeatedly admitted – the skilled artisan would not have had any reasonable expectation of success. *See* Pet. 17-18 (citing SA112-13). For example, Alphapharm states that "[t]he skilled artisan

would have understood that any attempt to maintain the activity of compound [b] would require ameliorating the compound's side effects by making conservative changes. . . ." Pet. 18 (citing Dr. Mosberg at SA112). But Alphapharm ignores the district court's rejection of Dr. Mosberg's theories (A20) and its contrary finding that "one skilled in the art would . . . make fairly radical changes in order to try to overcome the problems." A108.

Alphapharm's assertion that "[h]ere, the prior art repeatedly promoted substituted TZDs, including methyl and ethyl substitutions, and thus provided a reason to modify compound b with homologation and ring-walking to arrive at the claimed pioglitazone" (Pet. 16), is unsupported by any citation. In fact, that assertion is contrary to the record:

> [N]othing in the '200 and the '779 Patents, or in any other publication from Takeda, would have given one skilled in the art an expectation of success from the substitution of an ethyl for a methyl. In its patents, Takeda specifically claims a variety of substituents on identified systems. For example, the '779 Patent includes substituents on a pyridyl or thiazolyl group, noting that "[a]s examples of such substituents may be mentioned lower alkyls (e.g., methyl, ethyl, etc.), lower alkoxy groups (e.g., methoxy, ethoxy, etc.), halogens (e.g., chlorine, bromine, etc.) and hydroxyl."

A124; *see* A24-25. "There were literally *thousands* of different substituents that one of ordinary skill in the art could consider. . . ." A107 (emphasis added). Thus,

the '779 patent alone disclosed millions of possible variations. RA3541-43. And that was only one of many possible research paths. A16-17 (quoting A114). When viewed in the context of the prior art as a whole, this is a far cry from "a *finite number* of identified, *predictable* solutions." *KSR*, 127 S. Ct. at 1732 (emphases added).

The record evidence showed, the district court found, and the Federal Circuit affirmed that there was "nothing in the prior art to provide a reasonable expectation that adding a methyl group to compound b would reduce or eliminate its toxicity" or "that homologation would bring about a reasonable expectation of success." A21. Alphapharm simply failed to prove its case, does not effectively challenge the Federal Circuit's determination of no clear error, and thus has no legitimate legal issue to bring before this Court.

C. The *Eli Lilly* decision, from which this Court denied certiorari, is on point. In *Eli Lilly*, the claim at issue differed from the closest prior art by one methyl group, which is what Alphapharm contends (Pet. 17) is the case here. *See Eli Lilly*, 471 F.3d at 1377-78. Alphapharm attempts to distinguish *Eli Lilly* by asserting that "[in] *Eli Lilly*, *all* the prior art taught away from selecting an adjacent homolog as a lead compound." Pet. 23 (emphasis in original). That is a distinction without a difference – or merit. Nowhere in *Eli Lilly* did the court base its decision on a finding that "*all* of the prior art taught away." *Cf. id.* (emphasis in original). Rather in both this and the *Eli Lilly* case, the Federal Circuit affirmed factual determinations, based on the prior "art *as a whole*," that the defendant failed to prove its contention that a person of ordinary skill in

the art would have chosen the structurally closest prior art compound as a "beginning" or "lead" compound. *Eli Lilly*, 471 F.3d at 1377-78 (quoting *Eli Lilly & Co. v. Zenith Goldline Pharms.*, 364 F. Supp. 2d 820, 850 (S.D. Ind. 2005)); A15. Moreover, in *Eli Lilly*, the prior art, as a whole, taught away because it "expressed a preference" for substituents other than that claimed in the patent-in-suit. *Eli Lilly*, 471 F.3d at 1378-79 (quoting *Eli Lilly*, 364 F. Supp. 2d at 845). Here, not only did the prior art as a whole express a preference for myriad other directions, and specifically identify three compounds that are diverse from pioglitazone as "most favorable," but the prior art specifically "singled out" Alphapharm's suggested "lead" as a non-starter because a skilled artisan "would have been dissuaded from selecting a lead compound that exhibited negative effects, such as toxicity, or other adverse side effects, *especially one that causes 'considerable increases in body weight and brown fat weight.'*" A16 (emphasis added).

III. The Finding of Unexpected Results Requires Rejection of Alphapharm's Obviousness Challenge

Even if the Federal Circuit's rejection of the prima facie case were incorrect, which it is not, the judgment is correct. The Federal Circuit affirmed the district court's determination that "Takeda rebutted any presumed expectation that compound b and pioglitazone would share similar properties." A24. According to the district court:

> Even if Alphapharm had been able to show a prima facie case of obviousness, there is compelling and conclusive evidence that

> pioglitazone's non-toxicity was unexpected. Alphapharm is unable to overcome the extreme differences in the toxicity profiles between pioglitazone and prior art compound (b), whose modification it contends would have led to the discovery of pioglitazone.

A96. Alphapharm ignores both this finding and the Federal Circuit's discussion of unexpected results on pages A23-26 of the Opinion, and does not squarely challenge the Federal Circuit's ruling that "[t]he court's characterization of pioglitazone's unexpected results is not clearly erroneous." A24; *see In re Soni*, 54 F.3d 746, 749 (Fed. Cir. 1995) ("[W]hether an applicant made a showing of unexpected results is one of fact, subject to the clearly erroneous standard of review."); *see also In re Harris*, 409 F.3d at 1341. That ruling independently supports the judgment rejecting the invalidity challenge.

Alphapharm asserts that the '779 patent's prosecution history taught that "Adding Substituents to the Pyridyl Ring Would Have Resulted in Compounds with the Same *Antidiabetic Effect*," and that "making such conservative changes would not affect the compound's *antidiabetic use*." Pet. 19 (emphasis added). Alphapharm's argument focuses only on compound b's supposed efficacy, while altogether ignoring that compound's "extreme" toxicity. A159 n.105; A96-97; A127-28; *see* A24. That approach is improper. *See In re Ruschig*, 343 F.2d 965, 978 (C.C.P.A. 1965) (holding "[w]hile the evidence does show that the compound had a blood sugar level lowering property, it also disclosed that it was lethal, a fact omitted from the solicitor's argument. Very high toxicity, in our view, cancels out any

notion of anti-diabetic 'utility.'"). Instead, Alphapharm's burden was to prove by clear and convincing evidence that the invention *as a whole* would have been obvious at the time it was made to one of ordinary skill in the art. 35 U.S.C. § 103. The invention *as a whole* includes not only the structure of the compound, but *all* of its properties. As stated in the classic case of *In re Papesch*, 315 F.2d 381, 391 (C.C.P.A. 1963):

> From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing. The graphic formulae, the chemical nomenclature, the systems of classification and study such as the concepts of homology, isomerism, etc., are mere symbols by which compounds can be identified, classified, and compared. But a formula is not a compound and while it may serve in a claim to identify what is being patented, as the metes and bounds of a deed identify a plot of land, the thing that is patented is not the formula but the compound identified by it. And the patentability of the thing does not depend on the similarity of its formula to that of another compound but of the similarity of the former compound to the latter. There is no basis in law for ignoring any property in making such a comparison. An assumed similarity based on a comparison of formulae must give way to evidence that the assumption is erroneous.

Non-toxicity is a crucial pharmaceutical property. A16; A107. Alphapharm's attempt to ignore compound

b's extreme toxicity and paint compound b as exhibiting only the "most minor side effect" (Pet. 25) belies the record. Even Alphapharm's Rule 30(b)(6) designee, Dr. Rosenberg, characterized compound b as "active, but toxic." RA2231(195:15-16). As the district court found: "Compound (b) was a highly toxic compound, and nothing in the prior art would have led one skilled in the art to expect that the 5-ethyl on a 2-pyridyl ring would be non-toxic." A127-28; *see* A24; A96-97. Compound b caused statistically significant toxicity to the liver, heart and erythrocytes, in addition to causing cataracts. A23-24 (citing A59-65); RA4662. Pioglitazone was clear of adverse effects in all those tests; Takeda subjected fifty of its most promising compounds to a battery of toxicity tests, and of those pioglitazone was the only compound to emerge "clean." A66; RA4661; RA4692; *see* A23-24. As Alphapharm's 30(b)(6) designee admitted, pioglitazone is "'clearly superior' to compound (b) because of its non-toxicity."[7] A127; *see* RA2241(235:25-236:4). Alphapharm's own trial expert agreed. RA3177 (1238:16-23).

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7. Alphapharm cites *In re Coes*, 173 F.2d 1012, 1014 (C.C.P.A. 1949), for the proposition that "where the claimed invention does not exhibit 'markedly superior' properties over the prior art, the claim is obvious." Pet. 21. As an initial matter, *Coes* was distinguished in *Papesch*, 315 F.2d at 392. Moreover, the categorical pronouncement in *Coes* is a "generalization [that] should be avoided insofar as specific chemical structures are alleged to be *prima facie* obvious one from the other." *Grabiak*, 769 F.2d at 731. Fundamentally, however, Alphapharm's admission that pioglitazone is "clearly superior" to the closest prior art, in addition to the district court's finding regarding the "extreme differences" in the toxicity profiles between pioglitazone and compound b (A96; *see* A24; A127), dispatches Alphapharm's proposition, were it to apply.

These facts lead to two inescapable conclusions. First, pioglitazone was patentable even had Alphapharm succeeded in making out a prima facie case of obviousness. *See Adams*, 383 U.S. at 51. Second, this case is different from *KSR*, where there was no showing of unexpected results or secondary considerations of nonobviousness. 127 S. Ct. at 1745. Here, Takeda submitted "overwhelming," "compelling and conclusive" rebuttal evidence. *See* A95-96 (applying *Dillon*, 919 F.2d at 692-93) ("When rebuttal evidence is submitted, all evidence must be considered anew.") (citations omitted). The court considered Alphapharm's contentions of obviousness based on structural similarity (*e.g.*, A10-26 (affirming A90-132)), and the other evidence of record, including testimony of Takeda's well-qualified experts, along with Alphapharm's admissions and those of its expert. In light of all that evidence, the court concluded, and the Federal Circuit affirmed, that Takeda's "compelling and conclusive" (A95-96) evidence of unexpected results would have "rebutted any presumed expectation that compound b and pioglitazone would share similar properties." A24. Thus, Alphapharm's silence as to unexpected results renders its unfounded claims of error moot and inappropriate for review.

IV. Alphapharm's Suggestion that the Federal Circuit's Decision Will Have a Drastic Effect on "Thousands" of Cases Is Unfounded

Alphapharm tries to create the illusion of a case that warrants this Court's attention by characterizing the Federal Circuit's decision as "add[ing] an onerous new motivation requirement," and "creat[ing] a dangerous precedent for all chemical obviousness cases concerning pharmaceuticals." Pet. 24. A plain reading of the district court and Federal Circuit decisions, however, shows a simple application of *KSR*; Alphapharm's attempt to create a legal issue concerning an "onerous" motivation requirement has no basis in the court's decision.

Similarly, Alphapharm attempts to twist the court's straightforward analysis of the prior art into some new "dangerous" precedent concerning teaching away. Alphapharm contends that the decision below repudiated a previously "strict" "standard for 'teaching away.'" Pet. 24. It plainly did not. The court simply applied *KSR* and *Graham*. The district court rested its factual finding about the prior art on the very articulation of the standard for teaching away that Alphapharm accuses the Federal Circuit of improperly "abandon[ing]." *See* A92 ("Prior art teaches away from an invention 'when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of the applicant's invention.'") (citations omitted). The Federal Circuit did no more than affirm that finding, made under that standard, for "[w]hat the prior art teaches and whether it teaches away from the claimed invention are questions of fact." *In re Berg*, 320 F.3d at 1312.

CONCLUSION

For the foregoing reasons, Alphapharm's Petition should be denied.

Dated: February 27, 2008

Respectfully submitted,

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IN THE

Supreme Court of the United States

ALPHAPHARM PTY., LTD. and GENPHARM, INC.,

Petitioners,

v.

TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

SUPPLEMENTAL APPENDIX

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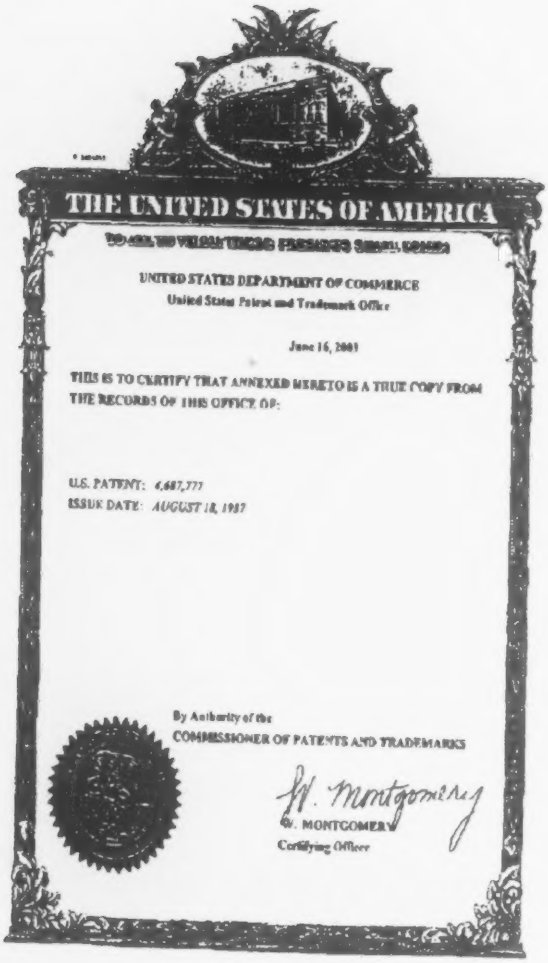

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June 16, 2001

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: *4,687,777*
ISSUE DATE: *AUGUST 18, 1987*

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M. Montgomery

M. MONTGOMERY
Certifying Officer

SA2

United States Patent [19]
Meguro et al.

[11] Patent Number: 4,687,777
[45] Date of Patent: Aug. 18, 1987

[54] THIAZOLIDINEDIONE DERIVATIVES, USEFUL AS ANTIDIABETIC AGENTS

[75] Inventors: Kenji Meguro, Nishinomiya; Takashi Fujita, Takarazuka, both of Japan

[73] Assignee: Takeda Chemical Industries, Ltd., Osaka, Japan

[21] Appl. No.: 820,390

[22] Filed: Jan. 17, 1986

[30] Foreign Application Priority Data

Jan. 19, 1985 [JP] Japan 60-8305

[51] Int. Cl.[4] A61K 31/44; C07D 417/04
[52] U.S. Cl. 514/343; 546/280
[58] Field of Search 546/280; 514/343

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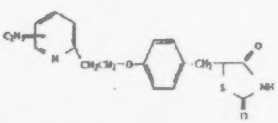
Attorney, Agent, or Firm—Woodcock, Lind & Ponnot

[57] ABSTRACT

Thiazolidinedione derivatives of the formula:



and pharmacologically acceptable salts thereof are novel compounds, which exhibit in mammals blood sugar- and lipid-lowering activity, and are of value as a therapeutic agent for treatment of diabetics and hyperlipemia.

5 Claims, No Drawings

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SA3

THIAZOLIDINEDIONE DERIVATIVES, USEFUL AS ANTIDIABETIC AGENTS

This invention relates to novel thiazolidinedione derivatives, a method of preparing them and antidiabetic agents containing same, which are utilized in the field of medicines.

A variety of biguanide and sulfonylurea derivatives have been used clinically as antidiabetic agents.

However, the biguanides are now scarcely used, because they tend to cause lactic acidosis, and use of the sulfonylureas, though they have strong hypoglycemic activities, requires sufficient precaution, because they frequently cause serious hypogly- cemia. Therefore, a new type of antidiabetic agent free from these defects has been desired.

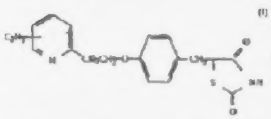
On the other hand, in Japanese Unexamined Patent Publication Nos. 224,36/1983 and 44586/1983, Chemical & Pharmaceutical Bulletin, 30, p. 3563 (1982), ibid. 30, p. 3580 (1982), and ibid. 32, p. 2267 (1984), reference is made to a variety of thiazolidinediones having blood glucose and lipid lowering actions. Antidiabetic activity of ciglitazone was also reported in Diabetes, 32, p. 804 (1983). These compounds, however, have not yet been put to practical use. As the reasons, (1) insufficient activities are found (2) serious toxicities may be mentioned.

The present inventors synthesized various compounds which are not concretely described in the above-mentioned publications of unexamined patent applications and have made studies on them to find the compounds exhibiting potent pharmacological effects with lower toxicity.

The present invention is to provide compounds which can be practically used as antidiabetic agents having a broad safety margin between pharmacological effect and toxicity or unfavorable side reactions.

The present invention relates to:

1. A compound of the formula



(I)

or a pharmacologically acceptable salt thereof,

2. an antidiabetic agent, which contains as the effective component a compound of the formula (I) or a pharmacologically acceptable salt thereof, and

3. a method of preparing a compound of the formula (I) or a pharmacologically acceptable salt thereof, which comprises hydrolyzing a compound of the formula

The compounds representable by the above formula (I) include, specific cases,

5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione,

5-[4-[2-(6-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione,

5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione,

5-[4-[2-(6-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione.

The compound (I) of this invention contains both basic nitrogen and acid nitrogen in its molecule, and it can be converted to a pharmacologically acceptable salt, when desired, by using a suitable acid or base.

Such acid salts are exemplified by mineral salts (e.g. hydrochloride, hydrobromide, sulfate, etc.), organic acid salts (e.g. succinate, maleate, fumarate, oxalate, tartrate, etc.) and sulfonates (e.g. methanesulfonate, benzenesulfonate, toluenesulfonate, etc.). Such basic salts are exemplified by alkali metal salts e.g. sodium salt, potassium salt, alkaline earth metal salts, e.g. calcium salt, etc. All of these salts can be prepared by per se known means.

The compound (I) of this invention or a pharmacologically acceptable salt thereof exhibits blood-glucose and blood-lipid lowering action with lower toxicity, and may be safely administered, orally or parenterally, as it is or advantageously as a pharmaceutical composition comprising an effective amount of the compound (I) or its pharmacologically acceptable salt and a pharmacologically acceptable carrier, excipient or diluent therefor, in the form of for example, powder, granule, tablet, hard capsule, soft capsule, dry syrup, suppository, injection or the like.

The composition for oral administration such as powder, granule, tablet, hard capsule, soft capsule and dry syrup may be prepared by a per se known conventional manner, and may comprise carriers, excipients or diluents conventionally used in the pharmaceutical art. For example, suitable carriers or excipients include lactose, starch, sugar, magnesium stearate, etc. As the excipients in the preparation of soft capsules, there may be used nontoxic, pharmaceutically acceptable oils and fats of animal, vegetable or mineral origin. The essential active ingredients are generally dissolved in these oils and fats before filling soft capsules therewith.

The compositions for parenteral administration may, for example, be injections and suppositories. The injectable preparations may be prepared in the form of solutions or suspensions. Injectable preparations in the form of aqueous solutions may be prepared by a conventional manner. The suppositories for rectal administration can be prepared by incorporating the compound (I) or its pharmacologically acceptable salt with a conventional suppository base.

The pharmaceutical composition of the present application can be used as an antidiabetic agent for mammals including man.

Oral administration to an adult patient is 0.05-10 mg/kg body weight/day, preferably 0.3-5 mg/kg body weight/day, and parenterally 0.01-10 mg/kg body weight/day, preferably 0.1 1.0 mg/kg body weight/day once daily or divided into 2-4 times a week.

The compound represented by the above-mentioned general formula (I) and pharmacologically acceptable salts thereof [hereinafter collectively referred to as "Compound (I)"] can be prepared by subjecting a compound represented by the general formula (II) to hydro-

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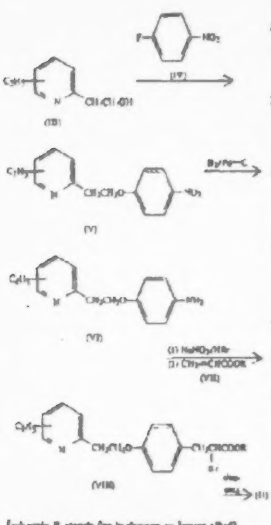
lysis. The reaction proceeds advantageously in a proper solvent by employing a mineral acid. The solvent is exemplified by alcohols (e.g. methanol, ethanol, propanol, butanol, isobutanol, 2-methoxyethanol, etc.), dimethylsulfoxide, sulfolane, dioxane, tetrahydrofuran, dimethoxyethane, etc., and the mineral acid is exemplified by hydrochloric acid, hydrobromic acid, sulfuric acid, etc. The reaction temperature ranges from 30° C. to 150° C. The reaction time is 0.5–20 hours.

The compound (I) or a pharmacologically acceptable salt thereof produced as mentioned above can be collected and purified by conventional means such as concentration, extraction, recrystallization, chromatography, etc.

The compound represented by the above-mentioned general formula (II) can be produced by the following reactions.



[wherein R stands for hydrogen or lower alkyl].

The lower alkyl group represented by R is exemplified by (C_{1-4}) alkyl such as methyl, ethyl, propyl, isopropyl and butyl.

The reaction for producing compound (V) from compound (III) and compound (IV) is conducted in the presence of, for example, sodium hydride. This reaction can be carried out in a solvent e.g. dimethylformamide and tetrahydrofuran at a temperature ranging from −10° C. to 30° C. The reaction from compound (V) to compound (VI) can easily be conducted by conventional catalytic reduction employing, for example, palladium-carbon as the catalyst. Compound (VI) may be isolated as the pure product or can be subjected to the subsequent reaction step without isolation and purification. Compound (VIII) can be produced by subjecting compound (VI) to diazotization in the presence of an aqueous solution of hydrobromic acid, then allowing the resultant to react with acrylic acid or its lower alkyl ester (VII) in the presence of a copper catalyst e.g. cuprous oxide, cupric oxide, cuprous chloride, cupric chloride, cuprous bromide, cupric bromide, etc. (Meerwein arylation). Compound (VIII) can be purified by e.g. chromatography, and subjected to the subsequent reaction without isolation or purification.

Compound (VIII) is then allowed to react with thiourea to give compound (II). This reaction is carried out usually in alcohols (e.g. methanol, ethanol, propanol, butanol, isobutanol, 2-methoxyethanol, etc.), dimethylsulfoxide, sulfolane, etc. The reaction temperature is usually 20°–180° C., preferably 60°–150° C. The amount of thiourea to be employed is 1–2 moles relative to one mole of compound (VIII).

In this reaction, as the reaction proceeds, hydrogen bromide is produced as the by product, and, for capturing this by-product, the reaction may be conducted in the presence of sodium acetate, potassium acetate, etc., in an amount of ca. by 1–4.5 mole relative to 1 mole of compound (VIII). The resultant compound (II) can be isolated, but may be subjected to the hydrolysis step directly without isolation.

(I) of the present invention has an excellent blood glucose and lipid lowering activity and is remarkably low in toxicity, which is supported by the following experimental data.

EXPERIMENTAL EXAMPLES

1. Blood Glucose and Lipid Lowering Activity in Mice

To male KK-A^y mice (8–10 weeks old, 5 mice/group), the test compounds (at three dosage levels) were given as a dietary admixture in CE-2 powdered diet (CLEA Japan) with free access to water for 4 days.

Blood samples were taken from the orbital vein on the 5th day.

Blood glucose and plasma triglyceride (TG) were determined by a glucose oxidase method and by using a commercially available assay kit, Clinotech TG-S (Iatron, Japan), respectively. Based on dose-response curves for blood glucose and plasma TG lowering activity, effective dose of each test compound in 25% decrease from the control value was calculated as the value of ED25 (mg/kg/day) The results are shown in Table 1.

2. Lipid Lowering Activity in Rats

Male Sprague-Dawley rats (7 weeks old, 5 rats/group) were maintained on the laboratory chow (CE-2, CLEA, Japan) with free access to water. All the test compounds (at three dosage levels) suspended in 5% gum arabic solution were forcedly administered to the animals orally for 4 days. Blood samples were taken from the tail vein on the 5th day. Plasma TG was determined using a commercially available assay kit, Clinotech TG-S (Iatron). Based on dose-response curves for lipid lowering activity, effective dose of each test compound in 25% decrease from the control value was calculated as the value of ED_{25} (mg/kg/day) The results are shown in Table 1.

3. Two-week Toxicity Study in Rats

Male and female Sprague-Dawley rats (5 weeks old, 5 rats/group) were maintained on the laboratory chow

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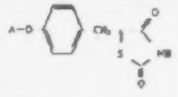
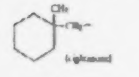
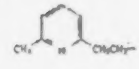
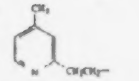
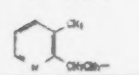
(CE-2, CLEA Japan) with free access to water. All the test compounds suspended in 5% gum arabic solution were forcedly administered orally to the animals for 2 weeks once daily. The dose was 100 mg/kg/day for every test compound. The animals were sacrificed in about 20 hours of fasting after termination of the two-week administration by withdrawing blood samples from the abdominal aorta using heparinized syringes under ether anesthesia. Liver and heart were removed and weighed. Hematology analysis was also carried out using an automatic cell counter. The data represent % increase or decrease from the control value (non-drug treated) as shown in Table I.

In Table I, Compound (I) of this invention is superior to the compounds (a), (c), (d) and (e) and comparable to the compound (b) in hypoglycemic and hypolipidemic activities, while showing extremely low toxicity as compared with the compounds (a), (b), (d) and (e). Such an effect as above caused by the introduction of an ethyl group is quite unexpected. Thus, compound (I) of the present invention exhibits excellent hypoglycemic and hypolipidemic activities, and little toxicity to internal organs and blood even by continuous administration for a long period of time. Therefore, compound (I) is of value as a therapeutic agent for Type II diabetes accom-

TABLE I



Compound A	Blood Glucose ($P(O)_2$)	14(12-Dpl		Two-week toxicity (rat, p.o.)					
				Liver weight		Heart weight		number of erythrocyte	
	mg/dl	mg/dl	%	δ	♀	δ	♀	δ	♀
(I)	b	b	b	−0.7	−2.5	+0.9	−1.9	−5.4	−0.7
(a) 	40	41	70	+8.6*	+10.1*	+12.0*	+4.8	+3.3	−0.2
(b) 	4	3	5	+3.0	+10.2**	+15.9**	+11.8**	−2.9	8.1**
(c)	20	20	—	+1.3	−5.2	+3.1	+1.0	−4.1	−6.0
(d) 	20	19	—	+6.8*	+8.4**	+3.1	+1.7*	−6.3	−2.3
(e) 	18	19	—	−1.1	+6.6**	+10.9	+9.8*	−8.7*	−7.0**

note: *P < 0.05, **P < 0.01

In Table I, Compound (I) is a compound under the coverage of the present invention, compounds (a) and (b) are known compounds concretely referred to in the Japanese unexamined Patent Publication No. 22636/1980.

While compounds (c), (d) and (e) are not concretely referred to in the above-mentioned patent publication, as they are cited for comparison, since they are similar to compound (I) of this invention in basic chemical structures. As is apparent from the experimental results given

painted by obesity or hyperlipemia in mammals including rats.

EXAMPLE 1

(a) To a solution of 2 (5-ethyl-2-pyridyl)ethanol (33.0 g) and 4-fluorobenzotrifluoride (47.8 g) in DMF (300 ml) was added portionwise under ice-cooling 60% sodium hydride in oil (16.0 g). The mixture was stirred under ice-cooling for one hour, then at room temperature for 30 minutes, poured into water and extracted with ether.

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The ether layer was washed with water and dried ($MgSO_4$). The solvent was evaporated off to give 4-[2-(5-ethyl-2-pyridyl)ethoxy]nitrobenzene as crystals (52.0 g, 62.9%). Recrystallization from ether-hexane gave colorless prisms, m.p. 53°-54° C.

(b) A solution of 4-[2-(5-ethyl-2-pyridyl)ethoxy]nitrobenzene (60.0 g) in methanol (500 ml) was hydrogenated at room temperature under one atmospheric pressure in the presence of 10% Pd-C (50% wet, 6.0 g). The catalyst was removed by filtration and the filtrate was concentrated under reduced pressure. The residual oil was dissolved in acetone (300 ml)-methanol (200 ml). To the solution was added a 47% HBr aqueous solution (152 g). The mixture was cooled, to which was added dropwise a solution of $NaNO_2$ (17.3 g) in water (30 ml) at a temperature not higher than 5° C. The whole mixture was stirred at 5° C. for 20 minutes, then methyl acrylate (112 g) was added thereto and the temperature was raised to 38° C. Cuprous oxide (2.0 g) was added to the mixture in small portions with vigorous stirring. The reaction mixture was stirred until nitrogen gas evolution ceased, and was concentrated under reduced pressure. The concentrate was made alkaline with concentrated aqueous ammonia, and extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). The solvent was evaporated off to leave methyl 2-bromo-3-[4-[2-(5-ethyl-2-pyridyl)ethoxy]phenyl]propionate as a crude oil (76.09 g, 95.7%). IR(neat)cm^{-1}: 1735. NMR δ(ppm) in $CDCl_3$: 1.21 (3H, t, J=7), 2.80 (2H, q, J=7), 3.0–3.6 (4H, m), 3.66 (3H, s), 4.30 (2H, t, J=7), 4.3 (1H, m), 6.7–7.5 (6H, m), 8.35 (1H, d, J=2).

(c) A mixture of the crude oil of methyl 2-bromo-3-[4-[2-(5-ethyl-2-pyridyl)ethoxy]phenyl]propionate (72.0 g) obtained in (b) thiourea (14.2 g), sodium acetate (15.1 g) and ethanol (300 ml) was stirred for 3 hours under reflux. The reaction mixture was concentrated under reduced pressure, and the concentrate was neutralized with a saturated aqueous solution of sodium hydrogencarbonate, to which were added water (200 ml) and ether (300 ml). The whole mixture was stirred for 10 minutes to yield 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2-imino-4-thiazolidinone as crystals (60.7 g, 523.0%). Recrystallization from methanol gave colorless prisms, m.p. 187°–188° C. (decomp.). Elemental analysis for $C_{19}H_{21}N_3O_2S$ Calcd.: C, 64.20; H, 5.95; N, 11.82. Found: C, 64.20; H, 5.84; N, 11.71.

(d) A solution of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2-imino-4-thiazolidinone (23.5 g) in 3N HCl (200 ml) was refluxed for 6 hours. The solvent was evaporated off under reduced pressure, and the residue was neutralized with a saturated aqueous solution of sodium hydrogencarbonate. The crystals (23.5 g, 97.5%) which precipitated were collected by filtration and recrystallized from DMF-H_2O to give 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione as colorless needles (20.5 g, 86.9%), m.p. 183°–184° C.

Elemental Analysis for $C_{19}H_{20}N_2O_3S$ Calcd.: C, 64.02; H, 5.66; N, 7.86. Found: C, 63.70; H, 5.80; N, 8.01.

(e) To a suspension of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione (356 mg) in methanol (10 ml) was added 28% sodium methylate/methanol solution (0.2 g) to make a solution. This solution was concentrated and diluted with ethyl ether to yield crystals. The crystals were collected by filtration and recrystallized from methanol-ethanol to give the sodium salt of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione as colorless crystals (298 mg, 73.8%), m.p. 262°–263° C. (decomp.).

Elemental analysis for $C_{19}H_{19}N_2O_3SNa$: Calcd.: C, 60.31; H, 5.06; N, 7.40. Found: C, 60.38; H, 5.02; N, 7.52.

EXAMPLE 3

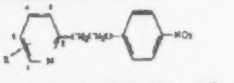
(1)	5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione	100 g
(2)	Lactose	70 g
(3)	Corn starch	15 g
(4)	Carboxymethyl cellulose calcium	94 g
(5)	Magnesium stearate	1 g
		280 g

The whole amounts of (1), (2) and (3) and 30 g of (4) were kneaded with water and dried in vacuo, followed by granulation. With the resultant granules were mixed 14 g of (4) and 1 g of (5) and the whole mixture was tableted with a tableting machine to give 1000 tablets 8 mm in diameter and each containing 100 mg of (1).

REFERENCE EXAMPLE 1

The compounds listed in Table 2 were prepared in accordance with Example 1-(a).

TABLE 2



R	mp	Recrystallization solvent	yield
3-CH_3	111–112° C.	ethyl acetate-hexane	62.9%
4-CH_3	75–76° C.	ethyl acetate-hexane	73.5%
5-CH_3	97–98° C.	ethyl acetate-hexane	72.3%

REFERENCE EXAMPLE 2

In accordance with Example 1-(b), the following compounds were prepared.

Methyl 2-bromo-3-[4-[2-(3-methyl-2-pyridyl)ethoxy]phenyl]propionate; IR(Nujol)cm^{-1}: 1735. NMR δ (ppm) in $CDCl_3$: 2.34 (3H, s), 3.10 (1H, dd, J=14 and 7), 3.25 (2H, t, J=6), 3.38 (1H, dd, J=14 and 7), 3.67 (3H, s), 4.29 (1H, t, J=7), 4.37 (2H, q, J=6), 6.8–7.5 (6H, m), 8.35 (1H, dd, J=5 and 2).

2-Bromo-3-[4-[2-(4-methyl-2-pyridyl)ethoxy]-phenyl]propionic acid methyl ester; IR(Nujol)cm^{-1}: 1735. NMR δ (ppm) in $CDCl_3$: 2.30 (3H, s), 3.10 (1H, dd, J=14 and 7), 3.36 (3H, t, J=7), 3.37 (1H, dd, J=14 and 7), 3.67 (3H, s), 4.30 (3H, t, J=7), 6.7–7.3(6H, m), 8.37 (1H, d, J=5).

REFERENCE EXAMPLE 3

A solution of 4-[2-(5-methyl-2-pyridyl)ethoxy]nitrobenzene (15.0 g) in methanol (150 ml) was subjected to catalytic reduction under 1 atmospheric pressure in the presence of 10% Pd-C (50% wet, 2.0 g). The catalyst was filtered off, and the filtrate was concentrated to give 4-[2-(5-methyl-2-pyridyl)ethoxy]aniline as crystals (12.3 g, 92.5%). Recrystallization from ethyl acetate-hexane gave colorless prisms, m.p. 74°–75° C.

Elemental analysis for $C_{14}H_{16}N_2O$: Calcd.: C, 73.66; H, 7.06; N, 12.27. Found: C, 73.84; H, 7.17; N, 12.06.

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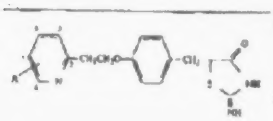
REFERENCE EXAMPLE 4

To a mixture of 4-[2-(5-methyl-2-pyridyl)ethoxy]benzaldehyde (12.8 g), 47% aqueous HBr solution (36.5 g) and methanol (40 ml)-acetone (80 ml) was added dropwise a solution of $NaNO_2$ (4.6 g) in water (10 ml) at 5° C. or below. The whole mixture was stirred at 5° C. for 20 minutes, then methyl acrylate (21.0 g) was added thereto and the temperature was raised to 38° C. Cuprous oxide (1.0 g) was added to the mixture in small portions with vigorous stirring. After nitrogen gas evolution had ceased, the reaction mixture was concentrated under reduced pressure. The concentrate was made alkaline with concentrated aqueous ammonia and extracted with ethyl acetate. The ethyl acetate layer was washed with water and dried ($MgSO_4$). The solvent was evaporated off to leave methyl 2-bromo-3-[4-[2-(5-methyl-2-pyridyl)ethoxy]phenyl]-propionate as a crude oil (17.3 g, 87.5%). IR(CH_2Cl_2)cm^{-1}: 1715. NMR δ (ppm) in $CDCl_3$: 2.27 (3H, s), 3.10 (1H, dd, J = 14 and 7), 3.72 (2H, t, J = 6), 3.80 (1H, dd, J = 14 and 7), 3.86 (3H, s), 4.29 (2H, t, J = 6), 4.32 (1H, t, J = 7), 6.7–7.5 (6H, m), 8.34 (1H, d, J = 2).

REFERENCE EXAMPLE 5

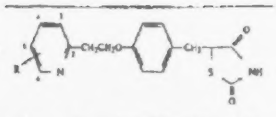
The compounds listed in Table 3 were prepared in accordance with Example 1-(a).



R	mp (decomp.)	Recrystallization solvent	yield
3-CH_3	116–118° C.	chloroform-methanol	75.1%
4-CH_3	150–161° C.	methanol	48.6%
5-CH_3	180–184° C.	chloroform-methanol	88.1%

REFERENCE EXAMPLE 6

The compounds listed in Table 4 were prepared in accordance with Example 1-(d).



R	mp	Recrystallization solvent	yield
3-CH_3	210–211° C.	DMF-water	85.7%
4-CH_3	178–179° C.	chloroform-methanol	72.4%

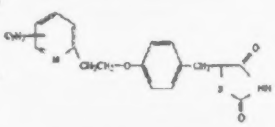
REFERENCE EXAMPLE 7

A mixture of 2-amino-5-[4-[2-(5-methyl-2-pyridyl)ethoxy]benzyl]-4-thiazolidinone (8.0 g), 2N HCl (90 ml) and ethanol (80 ml) was refluxed for 16 hours. The reaction solution was neutralized with a saturated aqueous solution of sodium hydrogencarbonate to yield crystals. The crystals were collected by filtration and recrystallized from ethanol to give 5-[4-[2-(5-methyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione as colorless prisms (7.0 g, 87.5%), m.p. 193°–193° C.

Elemental Analysis for $C_{21}H_{24}N_2O_3$: Calcd.: C, 63.36; H, 5.30; N, 8.10. Found: C, 63.22; H, 5.40; N, 8.11

We claim:

1. A compound of the formula:



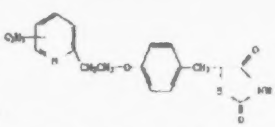
or a pharmacologically acceptable salt thereof.

2. A compound as claimed in claim 1, wherein the compound is 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione.

3. A compound as claimed in claim 1, wherein the compound is sodium salt of 5-[4-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione.

4. A compound as claimed in claim 1, wherein the compound is 5-[4-[2-(6-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione.

5. An antidiuretic composition which contains essentially of a compound of the formula:



or a pharmacologically acceptable salt thereof, in association with a pharmacologically acceptable carrier, excipient or diluent.

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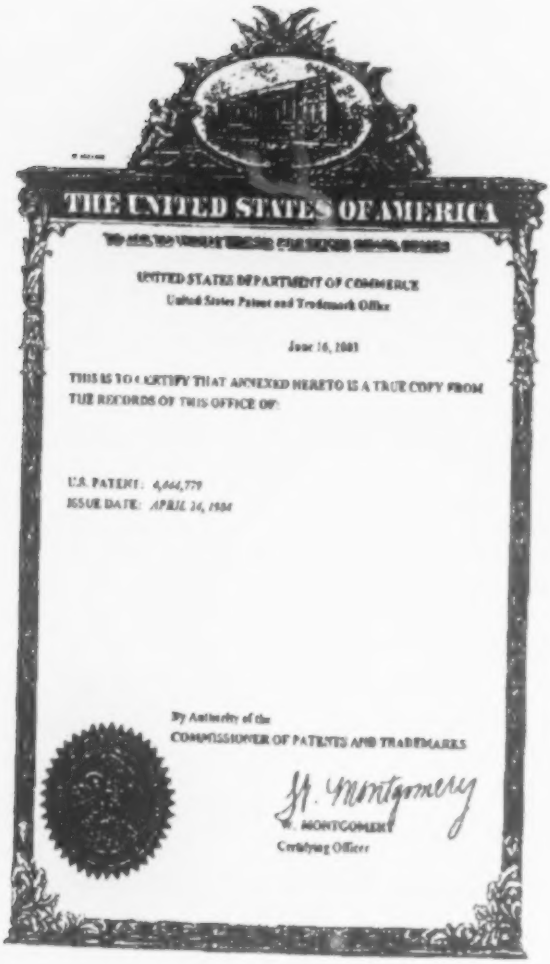

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United States Patent [19]
Kawamatsu et al.

[11] 4,444,779
[45] * Apr. 24, 1984

[54] THIAZOLIDINE DERIVATIVES

[75] Inventors: Yutaka Kawamatsu, Kyoto; Takaaki Fujita, Takarazuka, both of Japan

[73] Assignee: Takeda Chemical Industries, Ltd., Osaka, Japan

[*] Notice: The portion of the term of this patent subsequent to Jul. 20, 1999 has been disclaimed.

[21] Appl. No.: 478,013

[22] Filed: Mar. 15, 1983

Related U.S. Application Data

[62] Division of Ser. No. 295,093, Feb. 7, 1981, which is a division of Ser. No. 258,536, Apr. 29, 1981, Pat. No. 4,340,608, which is a division of Ser. No. 62,542, Jul. 27, 1979, Pat. No. 4,287,200.

[30] Foreign Application Priority Data

Aug. 4, 1978 [JP] Japan 53-95871

[51] Int. Cl.³ C07D 277/20; A61K 31/425
[52] U.S. Cl. 424/263; 424/270; 546/194; 548/208; 548/202; 548/203
[58] Field of Search 548/202, 203, 204; 424/263, 270; 546/208, 334

[56] References Cited

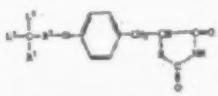
U.S. PATENT DOCUMENTS

4,340,608 7/1982 Kawamatsu et al. 424/263

Primary Examiner—Nicholas S. Rizzo
Attorney, Agent, or Firm—Wenderoth, Lind & Ponack

[57] ABSTRACT

Thiazolidine derivatives of the general formula:



[wherein R^1 is alkyl, cycloalkyl, phenylalkyl, phenyl, a five- or six-membered heterocyclic group having one or two hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur or a group of the formula

(where R^2 and R^3 are the same or different and each is lower alkyl or R^2 and R^3 are combined to each other either directly or as interrupted by a hetero-atom selected from the group consisting of nitrogen, oxygen and sulfur to form a five- or six-membered ring), R^0 means a bond or a lower alkylene group, L^1 and L^2 are the same or different and each is lower alkyl or L^1 and L^2 are combined to form an alkylene group, provided that when R^1 is other than alkyl, L^1 and L^2 may further be hydrogen, respectively] are novel compounds and useful as, for example, remedies for diabetes, hypolipidemia and so on of mammals including human beings.

8 Claims, No Drawings

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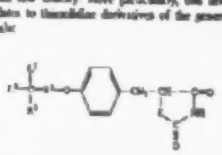
THIAZOLIDINE DERIVATIVES

This is a division of application Ser. No. 396,080 filed July 7, 1982, which is a division of application Ser. No. 258,554, filed Apr. 29, 1981, now U.S. Pat. No. 4,340,605, which in turn is a division of application Ser. No. 62,512 filed July 27, 1979, now U.S. Pat. No. 4,287,200.

This invention relates to novel thiazolidine derivatives having hypoglycemic and hypoglycemic activities with low toxicity. More particularly, this invention relates to thiazolidine derivatives of the general formula:



[wherein R^1 is alkyl, cycloalkyl, phenylalkyl, phenyl, a five- or six-membered heterocyclic group including one or two hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur, or a group of the formula

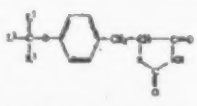
(where R^3 and R^4 are the same or different and each means lower alkyl or R^3 and R^4 are combined to each other either directly or as interrupted by a hetero-atom selected from the group consisting of nitrogen, oxygen and sulfur to form a five- or six-membered ring as taken together with the nitrogen atom adjacent to R^3 and R^4); L^1 is a bond or a lower alkylene group; L^2 and L^3 may be the same or different and each is lower alkyl or L^1 and L^2 are combined to each other to form an alkylene group, provided that when R^1 is other than alkyl, L^2 and L^3 may further be hydrogen, respectively].

Referring to the general formula (I), the alkyl group R^1 may be a straight-chain or branched alkyl of 1 to 10 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl and n-decyl; the cycloalkyl group R^1 may be a cycloalkyl group of 3 to 7 carbon atoms, such as cyclopropyl, cyclopentyl, cyclohexyl, and cycloheptyl; and the phenylalkyl group R^1 may be a phenylalkyl group of 7 to 11 carbon atoms such as benzyl and phenethyl. As examples of the heterocyclic group R^1 may be mentioned 5- or 6-membered groups each including 1 or 2 hetero-atoms selected from among nitrogen, oxygen and sulfur, such as pyridyl, thienyl, furyl, thiazolyl, etc. When R^1 is

the lower alkyls R^3 and R^4 may each be a lower alkyl of 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl and n-butyl. When R^3 and R^4 are combined to each other to form a 5- or 6-membered heterocyclic

group as taken together with the adjacent N atom, i.e. in the form of

the heterocyclic group may further include a hetero-atom selected from among nitrogen, oxygen and sulfur, as exemplified by piperidino, morpholino, pyrrolidino and piperazino. The lower alkylene group R^2 may contain 1 to 3 carbon atoms and, thus, may for example be methylene, ethylene or trimethylene. The bond R^2 is equivalent to the symbol "—" or the like which is used in chemical structural formulas, and when R^2 represents such a bond, the compound of general formula (I) is represented by the following general formula (II):



(II)

Thus, when R^2 is a bond, the atom adjacent thereto on both sides are directly combined together. As examples of the lower alkyls L^2 and L^3, there may be mentioned lower alkyl groups of 1 to 3 carbon atoms, such as methyl and ethyl. The alkylene group formed as L^2 and L^3 are joined together is a group of the formula —$(CH_2)_n$— [wherein n is an integer of 2 to 6.] The cycloalkyl, phenylalkyl, phenyl and heterocyclic groups mentioned above, as well as said heterocyclic group

may have 1 to 3 substituents in optional positions on the respective rings. As examples of such substituents may be mentioned lower alkyls (e.g. methyl, ethyl, etc.), lower alkoxy groups (e.g. methoxy, ethoxy, etc.), halogens (e.g. chlorine, bromine, etc.) and hydroxyl. The case also falls within the scope of the general formula [I] that an alkylenedioxy group of the formula —O—$(CH_2)_m$—O— [m is an integer of 1 or 2], such as methylenedioxy, is attached to the two adjacent carbon atoms on the ring to form an additional ring.

The compound (I) according to this invention can be converted to various salts by procedures known per se. For example, when the heterocyclic group R^1 includes a tertiary nitrogen atom, or R^1 means a group of the formula

the compound (I) can be converted to acid salts with acids, such as hydrochloric acid, sulfuric acid, acetic acid, oxalic acid, etc. When R^1 does not include a tertiary nitrogen atom, the compound may be converted to salts with cations such as a sodium ion, a potassium ion, a calcium ion, or an ammonium ion, etc.

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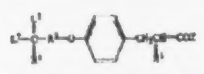
The thiazolidine derivative (I) according to this invention has activity to lower the blood sugar and triglyceride levels in mice (KKAy) with spontaneous diabetes and is expected to be of value in the treatment of hyperlipemia, diabetes and their complications in mammals including human beings. The compound (I) has low toxicity. For example, the LD$_{50}$ value of 5-[4-(1-methylcyclohexylmethyloxy)benzyl]thiazolidine-2,4-dione in a rat is more than 10 g/kg. (P.O.). The compound (I) may be orally administered in such dosage forms as tablets, capsules, powders, granules, etc. or by other routes in such forms as injections, suppositories, pellets and so on. Taking the treatment of hyperlipemia as an example, the compound may be orally or otherwise administered at a normal daily dose level of 50 mg to 1 gram per adult human. For the treatment of diabetes, the compound (I) may be orally or otherwise administered at a normal daily dose of 10 mg to 1 gram per adult human.

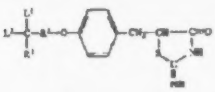
The thiazolidine derivative (I) of this invention may be produced, for example, by the following methods.

(1) The thiazolidine derivative (I) can be produced by the steps of reacting a compound of general formula (III) with thiourea to obtain an 2-iminothiazolidin-4-one derivative of general the formula (IV) and, then, hydrolyzing the last mentioned derivative (IV).



(III)

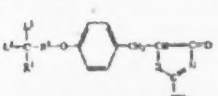
[wherein R^1, R^2, L^1 and L^2 have the meanings respectively defined hereinbefore; X^1 means halogen (e.g. chlorine, bromine, etc.), alkylsulfonyloxy (e.g. methylsulfonyloxy, etc.) or arylsulfonyloxy (e.g. toluenesulfonyloxy, etc.); Y is lower alkoxy (e.g. methoxy, ethoxy, etc.), hydroxyl, amino or a group of the formula —OM (M is, for example, an alkali metal) or, e.g. Na, K, etc., or NH$_4$]



(IV)

[wherein R^1, R^2, L^1 and L^2 have the meanings respectively defined hereinbefore]

The compound (IV) may tautomerically take the form as below:

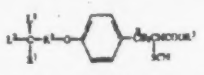


(IV')

[wherein R^1, R^2, L^1 and L^2 have the meanings respectively defined hereinbefore] The compound (IV') is also included within the scope of this invention. In this specification, the nomenclature and formula of these compounds are described on this as "2-iminothiazolidine derivatives" and as formula (IV), respectively.

The reaction between a compound (III) and thiourea is normally conducted in a solvent. As examples of such solvent may be mentioned alcohols (e.g. methanol, ethanol, propanol, butanol, ethylene glycol monomethyl ether, etc.), ethers (e.g. tetrahydrofuran, dioxane, etc.), acetone, dimethylsulfoxide, sulfolane, dimethylformamide, etc. While the relative amounts of starting materials need not be critically controlled, it is normally desirable to employ a slight excess of thiourea based on compound (III). Then, 1 to 2 molecular equivalents of thiourea is preferably employed relative to compound (III). While the conditions of reaction such as reaction temperature and time depend on such factors as the starting material, solvent, etc., this reaction is normally carried out at the boiling point of the solvent used or at 100° to 130° C. for a few to ten and odd hours. The sparingly soluble imino-compound (IV) is produced as the above manner. This imino-compound (IV) may be isolated prior to the following hydrolysis step or the reaction mixture containing (IV) may be directly hydrolyzed. In the hydrolysis step, the imino-compound (IV) is heated in a suitable solvent (e.g. mildsolvent) and in the presence of water and mineral acid. The acid just mentioned is added normally in a proportion of 0.1 to 10 molecular equivalents, preferably 0.2 to 3 equivalents, based on compound (III), while water is used normally in large excess based on compound (III). The heating time normally ranges from a few hours to 10 and odd hours.

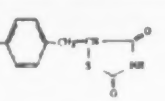
(2) The thiazolidine derivative (I) can further be produced by subjecting a compound of formula:



(V)

[wherein L^1, L^2, R^1 and R^2 have the meanings given above, and R^3 means alkyl having 1 to 4 carbon atoms (e.g. methyl, ethyl, n-propyl, n-butyl, t-butyl, etc.), aryl having 6 to 8 carbon atoms (e.g. tolyl, etc.) or aralkyl having 7 to 8 carbon atoms (e.g. benzyl, etc.)] to a cyclization reaction. This cyclization reaction is usually carried out by hydrolyzing a compound (V) with water. The hydrolysis is generally conducted in the presence of a catalyst, examples of which include hydrogen halides (e.g. hydrogen chloride, hydrogen bromide), mineral acids such as hydrochloric acid, sulfuric acid, etc. The catalyst may generally be used in an amount of 20 to 50 mol equivalents relative to the compound (V). This reaction may be conducted in the presence of an organic solvent such as alcohol (e.g. methanol, ethanol, etc.). While the reaction temperature varies with the type of catalyst used, the reaction may generally be carried out at a temperature ranging 50° to 150° C. The reaction time is usually in the range of 2 to 30 hours.

(3) The thiazolidine derivative (I) can also be produced by reacting compound of the formula:



(VI)

with a compound of the formula:

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(VII)

(wherein L^1, L^2, R^1 and R^2 have the meanings given above, and X^2 means a halogen atom such as chlorine, bromine, etc.) in the presence of a base. As the base, there may be mentioned sodium hydride, potassium carbonate, sodium carbonate, potassium hydroxide, sodium hydroxide, etc. This reaction is usually carried out in the presence of a solvent. As a suitable solvent, there may be mentioned dimethylformamide, dimethylsulfoxide, etc. The reaction temperature may be in the range of room temperature to 80° C.

The resulting thiazolidine derivative (I) can be isolated and purified by conventional procedures such as concentration at atmospheric or subatmospheric pressure, solvent extraction, crystallization, recrystallization, plastic transfer, chromatography, etc.

The compound (III) which is used as the starting material in the above preparation method (I) can be produced, for example, by the steps of dissolving the corresponding sulfide compound and subjecting the thiazo-compound to bromoxin oxydation.

The following reference and working examples are given to illustrate this invention in further detail.

REFERENCE EXAMPLE 1

In 200 ml of methanol is dissolved 19.0 g of 4-[2-(N,N-dimethylaminoethylthio)-benzoyl]benzonitrile and after 3 g of 10% Pd-C (50% wet) is added, catalytic reduction is carried out at atmospheric temperature and pressure. The reaction system absorbs about 4.4 l of hydrogen in 75 minutes. The catalyst is then filtered off, the filtrate is concentrated under reduced pressure and the oily residue is dissolved in a mixture of 300 ml methanol and 100 ml acetone. Following the addition of 21.3 ml of concentrated hydrochloric acid, the solution is cooled to 0° C. and a solution of 4.9 g sodium nitrite in 10 ml water is added dropwise at a temperature not exceeding 5° C. The mixture is stirred at 5° C. for 30 minutes, at the end of which time 33.3 g (34.9 ml) of methyl acrylate is added. The reaction mixture is heated to 35° C. and 1 g of cuprous oxide is added in small portions, whereupon the temperature of the reaction system rises to 44° C. with the evolution of nitrogen gas. The mixture is stirred for one hour and after the temperature has dropped to room temperature, it is allowed to stand overnight. The solvent is then distilled off under reduced pressure and the residue is made strongly basic with concentrated aqueous ammonia. Then, following the addition of water, extraction is carried out with ethyl acetate. The extract is washed with water, dried over sodium sulfate and distilled to remove the ethyl acetate. The oily residue is chromatographed on a column of 200 g silica gel, elution being carried out with ether-n-hexane (1:4). By the above procedure is obtained 10.7 g (44.8%) of methyl 3-chloro-3-[4-[2-(N,N-dimethylamino)-ethylthio]-benzoyl]-propionate.

IR (liquid film) $\nu_{max}^{cm^{-1}}$: 2945, 2820, 1745, 1675, 1595, 1250, 1170, 1020

NMR δppm $CDCl_3$: 0.93(6H, t), 1.2–1.36(6H, m), 2.52(4H, t), 2.82(2H, t), 3.0–3.92(2H, m), 3.92(3H, s), 4.0(2H, t), 4.4(1H, t), 6.75–7.38(4H, q)

EXAMPLE 1

(a) A mixture of 3.6 g of ethyl 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)-phenyl]-propionate, 0.73 g of thiourea and 3 ml of sulfolane is heated at 120° C. for 4 hours and after cooling, 15 ml of water is added. The oil is separated, ether is added to the oil and the crystalline insolubles (a) are separated from the solution (b) by filtration. The filtrate (b) is distilled to remove the solvent and the residue is run onto a column of 100 g silica gel, elution being carried out with chloroform. By the above procedure is obtained 1.7 g of 5-[4-(2-methyl-2-phenylpropyloxy)-benzyl]-thiazolidine-2,4-dione. m.p. 107°–108° C. (benzene-ligroin)

On the other hand, crystals (a) are recrystallized from ethanol-acetone (3:1) to obtain 1 g of 2-imino-5-[4-(2-methyl-2-phenylpropyloxy)-benzyl]-thiazolidin-4-one with a decomposition point of 210°–212° C. A 300 mg portion of this crystalline product is boiled with 2 ml of sulfolane and 2 ml of 6 N-HCl at 110° C. for 5 hours. After cooling, 50 ml of water is added and the resulting crystals are recrystallized from benzene-ligroin. By the above procedure is obtained 250 mg of 5-[4-(2-methyl-2-phenylpropyloxy)-benzyl]-thiazolidine-2,4-dione.

EXAMPLE 2

A mixture of 27 g of ethyl 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)-phenyl]-propionate, 11 g of thiourea and 60 ml of sulfolane is heated at 110° C. for 6 hours and, then, boiled with 30 ml of 2 N-sulfuric acid (or 2 ml of 6 N-HCl) for 16 hours. After cooling, 1 l of water is added and the oil is separated and allowed to stand for a while, whereupon crystals separate out. These crystals are recrystallized from benzene-ligroin. By the above procedure is obtained 15.9 g of 5-[4-(2-methyl-2-phenylpropyloxy)-benzyl]-thiazolidine-2,4-dione.

EXAMPLE 3

(a) 393 mg of 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)-phenyl]-propionic acid and 150 mg of thiourea are heated with 2 ml of sulfolane at 120° C. for 1.5 hours and, following the addition of 2 ml of 6 N-HCl, the mixture is further heated for 3 hours, at the end of which time 10 ml of water is added. The resulting crystals are recovered by filtration. By the above procedure is obtained 310 mg of 5-[4-(2-methyl-2-phenylpropyloxy)-benzyl]-thiazolidine-2,4-dione.

(b) The same procedure as that described in (a) is repeated except that 355 mg of sodium 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)-phenyl]-propionate is employed. By this procedure is obtained 330 mg of 5-[4-(2-methyl-2-phenylpropyloxy)-benzyl]-thiazolidine-2,4-dione.

(c) The same procedure as that described in (a) is repeated except that 332 mg of 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)-phenyl]-propionamide is employed. By this procedure is obtained 340 mg of 5-[4-(2-methyl-2-phenylpropyloxy)-benzyl]-thiazolidine-2,4-dione.

(d) In 10 ml of ethanol are dissolved 1.0 g of ω-bromo-2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)-phenyl]-propionate and 0.8 g of thiourea and the solution is heated for 3 hours, at the end of which time 50 ml of water is added.

By the above procedure is obtained 1.0 g of 2-imino-5-[4-(2-methyl-2-phenylpropyloxy)-benzyl]-thiazolidin-4-one.

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EXAMPLE 4

In 2 ml of dimethylsulfoxide are dissolved 208 mg of 3-bromo-3-[4-(4-chlorobenzyloxy)phenyl]propionic acid and 100 mg of thiourea, and the solution is heated at 140° C. for 3 hours. Then, after 0.5 ml of water is added, the solution is further heated for 5 hours. Then, 10 ml of water is added and the resulting crystals are recovered by filtration and recrystallized from benzene-n-hexane (1:1). By the above procedure is obtained 170 mg of 5-[4-(4-chlorobenzyloxy)benzyl]thiazolidine-2,4-dione.

EXAMPLE 5

1.9 g of ethyl 3-[4-(2-methyl-2-phenylpropyloxy)-phenyl]-2-thiocyanatopropionate is dissolved in 20 ml of ethanol and to the solution 20 ml of 6 N-hydrochloric acid is added. The mixture is refluxed for 24 hours. After cooling, water is added to the mixture. The mixture is subjected to extraction with ether. The extract is washed with water and then dried. After distilling off ether, the residue is crystallized from ether-n-hexane, whereby 710 mg of 5-[4-(2-methyl-2-phenylpropyloxy)-benzyl]thiazolidine-2,4-dione is obtained.

EXAMPLE 6

2.1 g of ethyl 2-methanesulfonyloxy-3-[4-(2-methyl-2-phenylpropyloxy)phenyl]propionate and 0.76 g of thiourea are added to 20 ml of sulfolane, and the mixture is heated at 120° C. with stirring for one hour. After adding 10 ml of 2 N-hydrochloric acid, the mixture is heated at 100° C. for 8 hours. After cooling, water is added to the mixture, and the mixture is subjected to extraction with ether. The extract is washed with water and dried. The ether is distilled off to give 1.3 g of 5-[4-(2-methyl-2-phenylpropyloxy)benzyl]thiazolidine-2,4-dione.

EXAMPLE 7

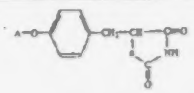
2.0 g of ethyl 2-methanesulfonyloxy-3-[4-(1-methyl-cyclohexylmethyloxy)phenyl]propionate and 760 mg. of thiourea are added to 20 ml of ethanol. The mixture is refluxed for 2 hours. To the mixture is added 10 ml of hydrochloric acid, and the mixture is further refluxed for 16 hours. After cooling, water is added to the mixture. The mixture is subjected to extraction with ethyl acetate. The extract is washed with water and dried. The ethyl acetate is distilled off to give 1.4 g of 5-[4-(1-methyl-cyclohexylmethyloxy)benzyl]thiazolidine-2,4-dione. Crystallization from 95% ethanol gives crystals melting at 150°–151° C.

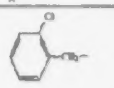
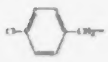
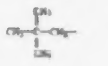
EXAMPLE 8

To 12 ml of dimethylsulfoxide is dissolved 1.12 g of 5-(4-hydroxybenzyl)thiazolidine-2,4-dione, and 400 mg of 50% sodium hydride in oil is added to the solution. The mixture is stirred at room temperature for 15 minutes, to which is added 0.81 g of 4-chlorobenzyl chloride. The whole mixture is stirred at 50° C. for 4 hours. Water is added to the mixture and the mixture is acidified with 2 N-hydrochloric acid. The mixture is subjected to extraction with ether. The extract is washed with water and dried. Ether is distilled off to give an oily substance. The oily substance is subjected to column chromatography on 30 g silica gel, elution being carried out with cyclohexane-ethyl acetate (2:1). By the above procedure there was obtained 425 mg of 5-[4-(4-chlorobenzyloxy)benzyl]thiazolidine-2,4-dione.

EXAMPLE 9

By procedures analogous to those described above in Examples 1 to 4, the following compounds were synthesized.



Compound No.	A	Recrystallization solvent	m.p. (°C.)	Analogous Example No.
1		Benzene-n-hexane	89–94	1,5
2		Benzene-cyclohexane	125–126	1
3		Benzene-Ligroin	126–128	1,3
4		Isopropyl ether	128–129	1

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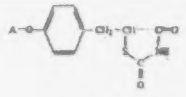
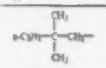
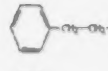
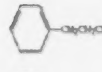
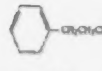
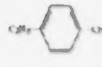


Compound No.	A	Recrystallization solvent	m.p. (°C.)	Analogous Example No.
5		Ether-n-hexane	98–104	1,2
6		Cyclohexane	108–110	1
7		Cyclohexane	106–108	2
8		Cyclohexane	101–103	1
9		Cyclohexane	101–102	2
10		Ether-n-hexane	101–103	1,2
11		n-Hexane	68–70	3
12		Benzene-ligroin	93–95	1,2
13		Ethyl acetate-cyclohexane	95–98	1
14		Ethyl acetate-cyclohexane	82–83	1
15		Ethyl acetate-n-hexane	110–114	3
16		Ether-n-hexane	93–95	3

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SA15

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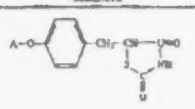
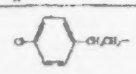
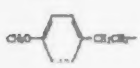
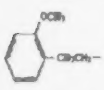
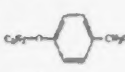
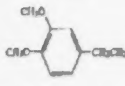
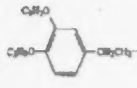
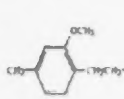
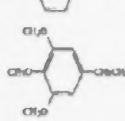
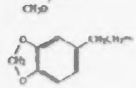
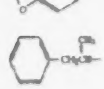


Compound No.	A	Recrystallization solvent	m.p. (°C.)	Analogous Example No(s).
17		Ethyl acetate	143–145	2
18		Ethyl acetate + hexane	144–146	2
19		Ethanol-hexane	72–73	2
20		Ethyl acetate-n-hexane	68–70	2
21		Ethanol-hexane	110–111	2
22		Oil (Diffuse reflection) 2900, 1730, 1700, 1600, 1460 cm^{-1}		3
23		Ethyl acetate-n-hexane	92–93	1
24		Ethyl acetate-n-hexane	104.5–105.5	2
25		Ethyl acetate-ether	131–133	2
26		Ethanol-hexane	84–85	1

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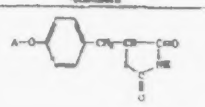
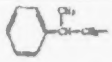
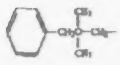
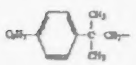
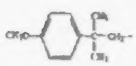
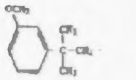
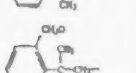
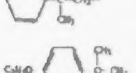
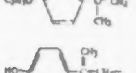
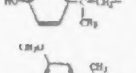


Compound No.	A	Recrystallization solvent	m.p. (°C.)	Analogous Example No(s).
27		Ethanol-hexane	66-67	13
28		Ethanol-hexane	107-108	1
29		Cyclohexane	106-107	2
30		Ethanol-hexane	104-105	2
31		Ethanol-hexane	107-108	2
32		Ethanol-hexane	66-67	2
33		Ethanol-hexane	110-111	2
34		Ethanol-hexane	65-66	2
35		Ether	171-172	2
36		Ethanol-hexane	104-105	1
37		Methanol	140-156	1

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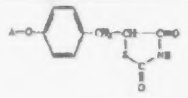
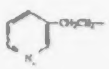
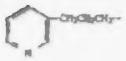
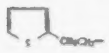
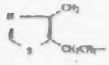
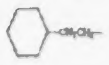


Compound No.	A	Recrystallization solvent	m.p. (°C.)	Analogous Example Method
38		Chloroform-methanol	175–176	12
39		Chloroform-methanol	176–177	1
40		DMF—H$_2$O	209–210	12
41		Methanol	167–168	1
42		Ethyl acetate-n-hexane	103–104	1
43		Ethanol-water	73–74	1
44		Ethanol-water	63–64	1
45		Ethanol	183–184.5	1
46		Cyclohexane	82–83	1
47		n-Propanol	131–132	12
48		Benzene-hexane	154–155	12

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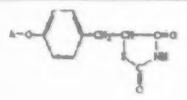
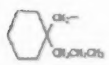


Compound No.	A	Recrystallization solvent	m.p. (°C.)	Analogous Example No.
47		Cyclohexane	124-125	1,5
49		Ligroin	88-89	1
51		n-Hexane	68-69	1
52		Benzene-ligroin	136-137	1
53		Ether-n-hexane	88-89	1
54		Ether-n-hexane	110-111	1

EXAMPLE 10

A mixture of 10.0 g methyl 2-chloro-2-[4-(2-morpholinoethyl)oxyphenyl]propionate and 6.44 g thiourea is heated in the presence of 100 ml of sulfolane at 120° C. for 4 hours. After cooling, a saturated aqueous solution of sodium hydrogen carbonate is added and the mixture is extracted with ethyl acetate. The extract is washed with water, dried over sodium sulfate and distilled to remove the ethyl acetate, whereupon 4.1 g (40.2%) of 2-imino-5-[4-(2-morpholinoethyl)oxyphenylthiazolidin-4-one is obtained as crystals. These crystals are recrystallized from ethyl acetate-methanol. Colorless needles, m.p. 159°-160° C.

In 20 ml of 2 N-HCl is dissolved 4.1 g of the above 2-imino-5-[4-(2-morpholinoethyl)oxybenzyl]thiazolidin-4-one and the solution is heated under reflux for 16 hours. After cooling, the reaction mixture is neutralized with a saturated aqueous solution of sodium hydrogen carbonate and extracted with ethyl acetate. The extract is washed with water, dried over sodium sulfate and distilled to remove the ethyl acetate, whereupon 3.5 g (90.7%) of 5-[4-(2-morpholinoethyl)oxybenzyl]thiazolidine-2,4-dione is obtained as crystals. These crystals are recrystallized from dimethylformamide-water. Colorless prisms, m.p. 188°-189° C.

EXAMPLE 11

A mixture of 9.0 g methyl 2-chloro-2-[4-(N,N-dimethoxyethoxyethyl)oxyphenyl]propionate and 2.4 g thiourea is heated in the presence of 100 ml of n-butanol at 100° C. for 15 hours. After cooling, the n-butanol is distilled off under reduced pressure, 100 ml of 2 N-HCl is added to the residue and the mixture is heated at 100° C. for 4 hours. After cooling, the reaction mixture is neutralized with a saturated aqueous solution of sodium hydrogen carbonate and extracted with ethyl acetate. The extract is washed with water, dried (over Na_2SO_4) and distilled to remove the ethyl acetate, whereupon 6.0 g (83.1%) of 5-[4-(2,N-dihydroxypropylamino)ethyloxybenzyl]thiazolidine-2,4-dione is obtained as crystals. These crystals are recrystallized from ethanol. Colorless prisms, m.p. 134° -135° C.

EXAMPLE 12

By procedures analogous to those described in Example 10 or 11, the following compounds were synthesized

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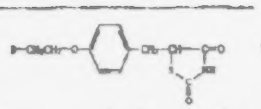


Compound No.	R	Recrystallization solvent	m.p. (°C.)	Analogous Example No.
1	.HCl	Ethanol	280–289	10, 11
2	.HCl	Ethanol	245–247	10, 11
3		Ethanol	120–122	11
4		Ethanol	130–135	11
5		Ethanol	98–99	10, 11
6	.HCl	Methanol	222–224	11
7	.HCl	Methanol	244–245	11

EXAMPLE 19

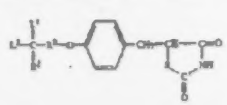
An example of practical recipe in which the compound of this invention is utilized as remedies for diabetes is as follows

(Tablets)		
(1)	5-[4-(2-methyl-5-benzoyloxybenzoyloxy)benzyl]thiazolidine-2,4-dione	10 mg
(2)	lactose	35 mg
(3)	corn starch	150 mg
(4)	microcrystalline cellulose	30 mg
(5)	magnesium stearate	5 mg
		230 mg per tablet

(1), (2), (3) and ½ quantity of (4) are thoroughly mixed, and then the mixture is granulated. Remaining ½ quantity of (4), and (5) are added to the granules and compressed into tablets. Thus prepared tablets can further be coated with a suitable coating agent.

What is claimed is:

1. A thiazolidine derivative of the formula:



wherein R^1 is a pyridyl group having 1 to 3 substituents selected from the group consisting of lower alkyls, halogens and hydroxyl on the ring, m is thienyl group having 1 to 3 substituents selected from the group consisting of lower alkyls, halogens and hydroxyl on the ring, R^3 means a bond or a lower alkylene group; L^1 and L^2 are the same or different and each is hydrogen, lower alkyl or L^1 and L^2 are combined to form an alkylene group.

2. A thiazolidine derivative as claimed in claim 1, each of L^1 and L^2 is hydrogen.

3. A thiazolidine derivative as claimed in claim 2, wherein R^3 is a lower alkylene group having 1 to 3 carbon atoms.

4. A compound as claimed in claim 1, wherein the compound is 5-[4-[2-(6-methyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione.

5. A compound as claimed in claim 1, wherein the compound is 5-[4-[2-(4-methyl-5-thienyl)ethoxy]benzyl]thiazolidine-2,4-dione.

6. A hypolipidemic and hypoglycemic pharmaceutical composition, which comprises, as an active ingredient, an effective amount of a thiazolidine derivative defined in claim 1 and a pharmaceutically acceptable carrier therefor.

* * * * *

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241-97-198
S3
4-62-47-3-1

REGULAR UTILITY

Form PTO-436
(Rev. 8/78)

4444779

SERIAL NUMBER (series of 1979)	PATENT DATE	PATENT NUMBER
476017	APR 24 1984	[redacted]

SERIAL NUMBER	FILING DATE	CLASS	SUBCLASS	GROUP ART UNIT	EXAMINER
476,017	03/15/83 RULE 60	568		122	

APPLICANT: YUTAKA KAWAMATSU, KYOTO, JAPAN; TOKUSHI FUJITA, TAKARAZUKA, JAPAN.

CONTINUING DATA********
VERIFIED THIS APPLN IS A DIV OF 06/596,723 [illegible]
WHICH IS A DIV OF 06/259,554 [illegible] PAT 4,340,605
WHICH IS A DIV OF 06/062,512 [illegible] PAT 4,287,200

FOREIGN/PCT APPLICATIONS********
VERIFIED JAPAN 55-[illegible]/1978 [illegible]

H12

Foreign priority claimed: yes / no — 35 USC 119 conditions met: yes / no — Verified and Acknowledged: Examiner's Initials

AS FILED

STATE OR COUNTRY	SHEETS DRAWING	TOTAL CLAIMS	INDEP. CLAIMS	FILING FEE RECEIVED	ATTORNEY'S DOCKET NO.
JPY	3	6	1	$ 336.00	

WENDEROTH, LIND AND PONACK
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~~2750 PA. AV.~~ N.W.
WASHINGTON, DC 20006

TITLE: [illegible]

U.S. DEPT. of COMM.-Pat. & TM Office — PTO-436L (Rev. 10-78)

241-97-198
83
4-62-47-3-1

PARTS OF APPLICATION FILED SEPARATELY

PREPARED FOR ISSUE

(Assistant Examiner) (Issue Clerk)

AT ALLOWANCE

SHEETS DRAWING	FIGURES DRAWING	CLAIMS	CLASS	SUBCLASS
4	16	16	424	263

EXAMINED AND PASSED FOR ISSUE

NICHOLAS S. RIZZO
PRIMARY EXAMINER
(Primary Examiner) (Art Unit)

(Claim for printing figure) | (Number of printed claims) | Issue fee due (ISL)

Division | Series | $500.

Notice of Allowance and issue fee due (ISL)

Date mailed: 11/24/83 | Date paid:

Form PTO-436-O.G. DEPT. OF COMMERCE (Rev. 6-78) PAT. & TM OFF

DISCLAIMER LABEL

SERIAL NO.	FILING DATE
476,017	3-15-83

A terminal disclaimer has been entered and recorded under 35 U.S.C. 253 to date this by Patent Issue Division.

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SA21

476017

3/18/83 BW 5/3/83

MAR 15 1983

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of :
YUTAKA KAWAMATSU ET AL. :
Filed March 15, 1983 : Group Art Unit 122
THIAZOLIDINE DERIVATIVES : Examiner N. Rizzo
[This is a Divisional of :
Serial No. 396,093 :
Filed July 7, 1982] :

PRELIMINARY AMENDMENT

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS

WASHINGTON, D.C.

Sir:

Kindly amend the above-identified application as follows:

In the Specification:

Page 4, line 11, after "as" insert -- a -- and change "potassiumion" to -- a potassium ion --;

line 12, change "calciumion, ammoniumion" to -- a calcium ion, or an ammonium ion --;

line 19, after "example" insert -- , the -- and change "valule" to -- value --;

line 21, after "in" insert -- a --.

Page 5, line 9, after "general" insert -- the --.

Page 7, line 12, after "to" insert -- a --;

line 19, change "equivalent" to -- equivalents --;

line 21, after "of" insert -- an --.

Page 8, line 7, after "means" insert -- a --;

line 8, change "are" to -- may be --;

line 12, change "are" to -- may be --.

Page 9, line 16, after "Following" insert -- the --.

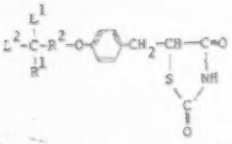
Page 10, line 2, after "following" insert -- the --.

Page 12, line 1, after "following" insert -- the --.

In the Claims:

Cancel Claims 1, 3, 4 and 7 and substitute the following Claims therefor:

10. A thiazolidine derivative of the formula:



wherein R^1 is a pyridyl group having 1 to 3 substituents selected from the group consisting of lower alkyls, halogens and hydroxyl on the ring, or a thiazolyl group having 1 to 3 substituents selected from the group consisting of lower alkyls, halogens and hydroxyl on the ring; R^2 means a bond or a lower alkylene group; L^1 and L^2 are the same or different and each is hydrogen, lower alkyl or L^1 and L^2 are combined to form an alkylene group.

11. A thiazolidine derivative as claimed in Claim 10, each of L^1 and L^2 is hydrogen.

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Bi Canceled

3
12. A thiazolidine derivative as claimed in Claim 10, wherein R^2 is a lower alkylene group having 1 to 3 carbon atoms.

4
13. A compound as claimed in Claim 10, wherein the compound is 5-[4-[2-(6-methyl-2-pyridyl)ethoxy]benzyl]thiazolidine-2,4-dione.

5
14. A compound as claimed in Claim 10, wherein the compound is 5-[4-[2-(4-methyl-5-thiazolyl)ethoxy]benzyl]thiazolidine-2,4-dione.

15. A hypolipidemic and hypoglycemic pharmaceutical composition, which comprises, as an active ingredient, an effective amount of a thiazolidine derivative defined in Claim 10.

REMARKS

The present Preliminary Amendment is submitted in an effort to place the application in optimum form for examination purposes.

The Specification has been amended to correct minor grammatical errors therein, which amendments are precisely the same as those presented in the previous applications including Serial No. 396,093.

In respect to the Claims, these Claims are essentially directed to the case wherein R^1 is a pyridyl group or a thiazolyl group which has 1 to 3 substituents on the rings of the pyridyl and thiazolyl groups, said substituents selected from lower alkyls, halogens and hydroxyl. Support for these substituents may be found on Page 3 of the Specification.

SA24

Claims 11 and 12 are simply narrowed embodiments restricting the L^1, L^2 and R^2 groups to cover preferred embodiments.

The compounds of Claims 13 and 14 are specifically disclosed in Example 9 of the original Specification as Compound Nos. 42 and 45, respectively.

In connection with the above, it must be pointed out that a Restriction Requirement was required in the first filed Kawamatsu application, Serial No. 62,512, now USP 4,287,208 in Paper No. 6 of that application. One of the groups of compounds restricted out is the case where R^1 represents pyridyl or thiazolyl and these compounds were claimed in USP 4,340,605, which was a divisional of the first filed application. However, in respect to the latter patent, it appears that the Claims do not cover the case wherein the pyridyl or thiazolyl groups may be substituted as disclosed in the original application. In this connection, as it turns out, the compounds in which these heterocyclic rings are substituted have become important, especially Compound 42 in Example 9.

In a brief discussion with the Examiner handling the parent application, it was thought best to file a Divisional application as has been done herein and to possibly file a Terminal Disclaimer at a later date.

It is respectfully requested that the present amendment be entered and be allowed. A Terminal Disclaimer will undoubtedly be required and will be filed at a later date, if necessary.

Respectfully submitted,

YUTAKA KAWAMATSU ET AL.

By John T. Pedigan
John T. Pedigan
Registration No. 24387
Attorney for Applicants

JTP/njp
Washington, D.C.
Tel. (202) 393-5150
March 15, 1983

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P. Webster

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

P. Webster 10/18/83

In re Application of

YUTAKA KANAMATSU ET AL.

Serial No. 476,017 — Group Art Unit 122

Filed March 15, 1983 — Examiner N. Rizzo

THIAZOLIDINE DERIVATIVES

AMENDMENT

HONORABLE COMMISSIONER OF PATENTS AND TRADEMARKS

WASHINGTON, D.C.

Sir:

In response to the Official Action of July 8, 1983, kindly amend the above-identified application as follows:

In the Claims:

Amend Claim 15 as follows:

C1

~~15.~~ (amended) A hypolipidemic and hypoglycemic pharmaceutical composition, which comprises, as an active ingredient, an effective amount of a thiazolidine derivative defined in ~~claim 14~~ and a pharmaceutically acceptable carrier therefor.

REMARKS

Further and favorable reconsideration is respectfully requested.

Claim 15 has been amended by stipulating that a "pharmaceutically acceptable carrier" is included in the composition claim. Support for this amendment is evident from the whole tenor of the Specification. Note, for example, Pages 4 and 5 of the Specification. By this amendment to the Claims, it is deemed that the rejection of Claim 15 in failing to point out the "other" components of the composition has been overcome.

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The rejection of Claims 10-15 on the ground of double patenting over U.S.P. 4,340,605 is respectfully traversed.

In order to overcome this rejection, a Terminal Disclaimer is enclosed herewith, thereby overcoming any extension of monopoly, which is the chief concern in such double patenting rejection. In a recent telephonic interview, the Examiner indicated that such Terminal Disclaimer should overcome this rejection.

The Claims have been rejected under 35 USC 112 as not claiming the invention primarily on the basis that no clear support for the substituted compounds now claimed exist in the Specification. In this connection, R^1 has been claimed as being a pyridyl group or a thiazolyl group containing a narrow group of constituents selected from lower alkyls, haloyens and hydroxyl. Full support for this claim language may be found on Page 3 of the Specification.

In respect to the compounds numbered 13 and 14, these compounds are specifically disclosed in Example 9 of the original Specification as compound numbers 42 and 45, respectively. Thus, full support for Claims 13 and 14 may be found in the Specification.

In respect to the Examiner's contention that no clear support for the substituted compounds can be found in the Specification, this has been rebutted by a reading of the specific examples as pointed out above. Moreover, it is well established that each and every member of a Markush grouping need not be set forth by way of specific examples, especially when the Markush group grouping, i e. the substituents in this case, actually cover a relatively narrow and well defined group of constituents. Moreover, there should

no reason in the instant case for the Examiner to doubt that the claimed compounds having the specified substituent would function as a hypolipidemic and hypyglycemic agent as specified in the instant disclosure. See In re Marzocchi et al. 169 USPQ 367.

In discussing this application with the Examiner to clarify matters, it was indicated that the above arguments, coupled with the Terminal Disclaimer and amendment to Claim 15 would undoubtedly place the application in allowable form. Accordingly, allowance of the application is respectfully solicited.

Respectfully submitted,

YUTAKA KAWAMATSU ET AL.

By John T. Fedigan
John T. Fedigan
Registration No. 24347
Attorney for Applicants

JTF/ajp
Washington, D.C.
Tel. (202)393-5150
September 13, 1983

A check covering the Patent Office fee of $50.00 for filing the enclosed Terminal Disclaimer accompanies this response.

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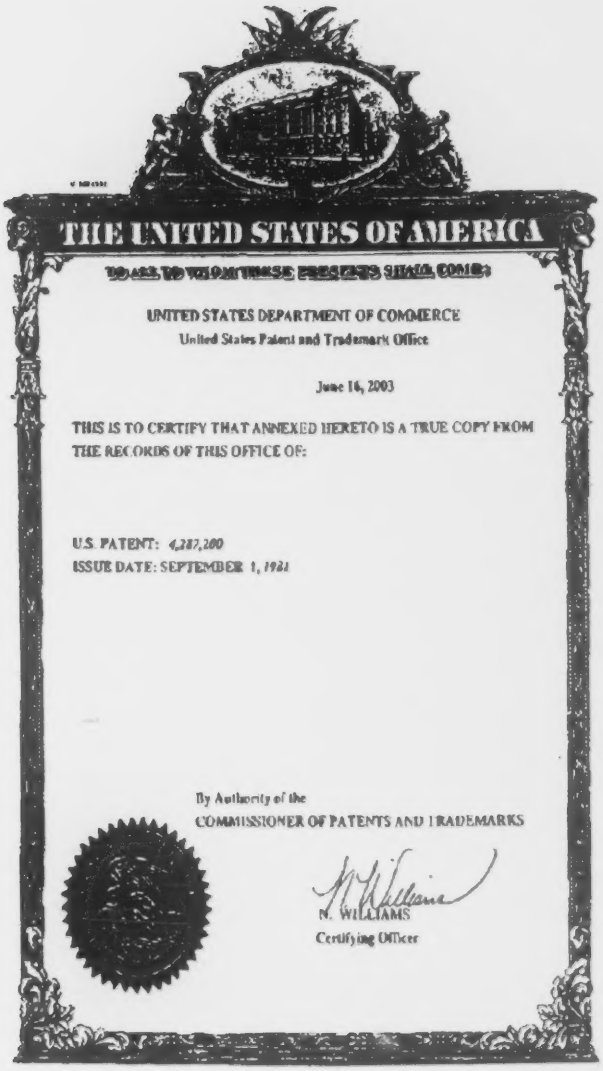


THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office

June 16, 2003

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THIS OFFICE OF:

U.S. PATENT: 4,287,200
ISSUE DATE: SEPTEMBER 1, 1981

By Authority of the
COMMISSIONER OF PATENTS AND TRADEMARKS

N. WILLIAMS
Certifying Officer

SA29

United States Patent [19]

Kawamura et al.

[11] 4,287,200

[45] Sep. 1, 1981

[54] THIAZOLIDINE DERIVATIVES

[75] Inventors: Takeo Kawamura, Kyoto; Takeshi Fujita, Takarazuka, both of Japan

[73] Assignee: Takeda Chemical Industries, Ltd., Osaka, Japan

[21] Appl. No.: 64,511

[22] Filed: Jul. 27, 1979

[30] Foreign Application Priority Data

Aug. 4, 1978 [JP] Japan 53-95473

[51] Int. Cl.³ C07D 277/04

[52] U.S. Cl. 424/270; 548/183; 546/194; 548/202

[58] Field of Search 548/183, 202; 424/270

[56] References Cited

U.S. PATENT DOCUMENTS

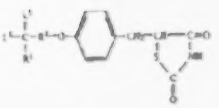
3,823,153 7/1974 Dimond et al. 548/183

Primary Examiner—Nicholas S. Rizzo

Attorney, Agent, or Firm—Wenderoth, Lind & Ponack

[57] ABSTRACT

Thiazolidine derivatives of the general formula:



[wherein R^1 is alkyl, cycloalkyl, phenylalkyl, phenyl, a five- or six-membered heterocyclic group containing one or two hetero-atoms selected from the group consisting of nitrogen, oxygen and sulfur or a group of the formula

(wherein R^3 and R^4 are the same or different and each a lower alkyl or R^3 and R^4 are combined to each other either directly or as interrupted by a hetero atom selected from the group consisting of nitrogen, oxygen and sulfur to form a five- or six-membered ring); R^2 means a bond or a lower alkylene group; L^1 and L^2 are the same or different and each a lower alkyl or L^1 and L^2 are combined to form an alkylene group, provided that when R^1 is other than alkyl, L^1 and L^2 may further be hydrogen, respectively] are novel compounds and useful as, for example, remedies for diabetes, hyperlipemia and so on of mammals including human beings.

8 Claims, No Drawings

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THIAZOLIDINE DERIVATIVES

This invention relates to novel thiazolidine derivatives having hypolipidemic and hypoglycemic activities and low toxicity. More particularly, this invention relates to thiazolidine derivatives of the general formula:

(I)

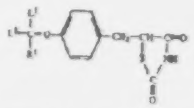
[wherein R' is alkyl, cycloalkyl, phenylalkyl, phenyl, a free- or an unreduced heterocyclic group including one or two hetero atoms selected from the group consisting of nitrogen, oxygen and sulfur, or a group of the formula

(where R' and R'' are the same or different and each means lower alkyl or R' and R'' are combined to each other either directly or as interrupted by a hetero-atom selected from the group consisting of nitrogen, oxygen and sulfur to form a five- or six-membered ring as taken together with the nitrogen atom adjacent to R' and R''; R' is a bond or a lower alkylene group; L' and L'' may be the same or different and each is lower alkyl or L' and L'' are combined to each other to form an alkylene group, provided that when R' is other than alkyl, L' and L'' may further be hydrogen, respectively].

Referring to the general formula (I), the alkyl group R' may be a straight-chain or branched alkyl of 1 to 10 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, t-butyl, n-pentyl, i-pentyl, n-hexyl, n-heptyl, n-octyl, n-nonyl and n-decyl; the cycloalkyl group R' may be a cycloalkyl group of 3 to 7 carbon atoms, such as cyclopropyl, cyclopentyl, cyclohexyl and cycloheptyl; and the phenylalkyl group R' may be a phenylalkyl group of 7 to 11 carbon atoms such as benzyl and phenethyl. As examples of the heterocyclic group R' may be mentioned 5- or 6-membered groups each including 1 or 2 hetero-atoms selected from among nitrogen, oxygen and sulfur, such as pyridyl, thienyl, furyl, thiazolyl, etc. When R' is

the lower alkyls R' and R'' may each be a lower alkyl of 1 to 4 carbon atoms, such as methyl, ethyl, n-propyl, i-propyl and n-butyl. When R' and R'' are combined to each other to form a 5- or 6-membered heterocyclic group as taken together with the adjacent N atom, it is the form of

this heterocyclic group may further include a hetero-atom selected from among nitrogen, oxygen and sulfur, as exemplified by piperidine, morpholine, pyrrolidine and piperazine. The lower alkylene group R' may contain 1 to 3 carbon atoms and, thus, may for example be methylene, ethylene or trimethylene. The bond R' is equivalent to the symbol "-", "=" or the like which is used in chemical structural formulas, and when R' represents such a bond, the compound of general formula (I) is represented by the following general formula (II):



(II)

Thus, when R' is a bond, the atoms adjacent thereto on both sides are directly combined together. As examples of the lower alkyls L' and L'', there may be mentioned lower alkyl groups of 1 to 3 carbon atoms, such as methyl and ethyl. The alkylene group formed as L' and L'' are joined together is a group of the formula —$(CH_2)_n$— [where n is an integer of 2 to 6]. The cycloalkyl, phenylalkyl, phenyl and heterocyclic groups mentioned above, as well as said heterocyclic group

may have 1 to 3 substituents in optional positions on the respective rings. As examples of such substituents may be mentioned lower alkyls (e.g. methyl, ethyl, etc.), lower alkoxy groups (e.g. methoxy, ethoxy, etc.), halogens (e.g. chlorine, bromine, etc.) and hydroxyl. The case also falls within the scope of the general formula [I] that an alkylenedioxy group of the Formula —O—$(CH_2)_m$—O— [m an integer of 1 to 3], such as methylenedioxy, is attached to the two adjacent carbon atoms on the ring to form an additional ring.

The compound (I) according to this invention can be converted to various salts by procedures known per se. For example, when the heterocyclic group R' includes a tertiary nitrogen atom, or R' means a group of the formula

the compound (I) can be converted to acid salts with acids, such as hydrochloric acid, sulfuric acid, acetic acid, oxalic acid, etc. When R' does not include a tertiary nitrogen atom, the compound may be converted to

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salts with cations such as a sodium ion, a potassium ion, a calcium ion, or an ammonium ion, etc.

The thiazolidine derivative (I) according to this invention has activity to lower the blood sugar and triglyceride levels in mice (KK-Ay) with spontaneous diabetes and is expected to be of value in the treatment of hyperlipemia, diabetes and their complications in mammals including human beings. The compound (I) has low toxicity. For example, the LD_{50} value of 5-[4-(5-methyl-2-phenyl-4-oxazolylmethoxy)benzyl]thiazolidine-2,4-dione in a rat is more than 10 g/kg. (P.O.). The compound (I) may be orally administered in such dosage forms as tablets, capsules, powders, granules, etc. or by other routes in such forms as injections, suppositories, pellets and so on. Taking the treatment of hyperlipemia as an example, the compound may be orally or otherwise administered at a normal daily dose level of 50 mg to 1 gram per adult human. For the treatment of diabetes, the compound (I) may be orally or otherwise administered at a normal daily dose of 10 mg to 1 gram per adult human.

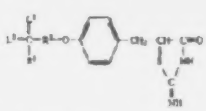
The thiazolidine derivative (I) of this invention may be produced, for example, by the following methods.

(1) The thiazolidine derivative (I) can be produced by the steps of reacting a compound of general formula (III) with thiourea to obtain an 2-iminothiazolidine derivative of general the formula (IV) and, then, hydrolyzing the last-mentioned derivative (IV).

(III)

[wherein R^1, R^2, L^1 and L^2 have the meanings respectively defined hereinbefore; X^1 means halogen (e.g. chlorine, bromine, etc.), alkylsulfonyloxy (e.g. methylsulfonyloxy, etc.) or arylsulfonyloxy (e.g. toluenesulfonyloxy, etc.); Z is lower alkoxy (e.g. methoxy, ethoxy, etc.), hydroxyl, amino or a group of the formula —OM (M is, for example, an alkali metal atom, e.g. Na, K, etc., or NH_4)]

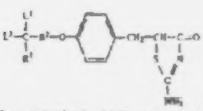
(IV)



[wherein R^1, R^2, L^1 and L^2 have the meanings respectively defined hereinbefore]

The compound (IV) may tautomerically take the form as below:

(IV)

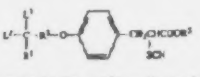


[wherein R^1, R^2, L^1 and L^2 have the meanings respectively defined hereinbefore] The compound (IV) is also included within the scope of this invention. In this specification, the nomenclature and formula of these compounds are described en bloc as "2-iminothiazolidine derivative" and as formula (IV), respectively.

The reaction between a compound (III) and thiourea is normally conducted in a solvent. As examples of such solvent may be mentioned alcohols (e.g. methanol, ethanol, propanol, butanol, ethylene glycol monomethyl ether, etc.), ethers (e.g. tetrahydrofuran, dioxane, etc.), acetone, dimethylsulfoxide, sulfolane, dimethylformamide, etc. While the relative amounts of starting materials need not be critically controlled, it is normally desirable to employ a slight excess of thiourea based on compound (III). Thus, 1 to 2 molecular equivalents of thiourea is preferably employed relative to compound (III). While the conditions of reaction such as reaction temperature and time depend on such factors as the starting material, solvent, etc., the reaction is normally carried out at the boiling point of the solvent used or at 80° to 150° C. for a few to ten and odd hours. The sparingly soluble imino-compound (IV) is produced in the above manner. This imino-compound (IV) may be isolated prior to the following hydrolysis step or the reaction mixture containing (IV) may be directly hydrolyzed. In the hydrolysis step, the imino-compound (IV) is heated in a suitable solvent (e.g. sulfolane) and in the presence of water and mineral acid. The acid just mentioned is added normally in a proportion of 0.1 to 10 molecular equivalents, preferably 0.2 to 3 equivalents, based on compound (III), while water is used normally in large excess based on compound (III). The heating time normally ranges from a few hours to 10 and odd hours.

(2) The thiazolidine derivative (I) can further be produced by subjecting a compound of formula

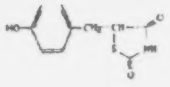
(V)



[wherein L^1, L^2, R^1 and R^2 have the meanings given above, and R^3 means alkyl having 1 to 4 carbon atoms (e.g. methyl, ethyl, n-propyl, n-butyl, t-butyl, etc.), aryl having 6 to 8 carbon atoms (e.g. tolyl, etc.) or aralkyl having 7 to 8 carbon atoms (e.g. benzyl, etc.)] to a cyclization reaction. This cyclization reaction is usually carried out by hydrolyzing a compound (V) with water. The hydrolysis is generally conducted in the presence of a catalyst, examples of which include hydrogen halides (e.g. hydrogen chloride, hydrogen bromide), mineral acids such as hydrochloric acid, sulfuric acid, etc. The catalyst may generally be used in an amount of 20 to 50 mol equivalents relative to the compound (V). This reaction may be conducted in the presence of an organic solvent such as alcohol (e.g. methanol, ethanol, etc.). While the reaction temperature varies with the type of catalyst used, the reaction may generally be carried out at a temperature ranging 50° to 150° C. The reaction time is usually in the range of 2 to 30 hours.

(3) The thiazolidine derivative (I) can also be produced by reacting compound of the formula:

(VI)



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with a compound of the formula

(VII)

(wherein L^1, L^2, R^1 and R^2 have the meanings given above, and X^2 means a halogen atom such as chlorine, bromine, etc.) in the presence of a base. As the base, there may be mentioned sodium hydride, potassium carbonate, sodium carbonate, potassium hydroxide, sodium hydroxide, etc. This reaction is usually carried out in the presence of a solvent. As a suitable solvent, there may be mentioned dimethylformamide, dimethylsulfoxide, etc. The reaction temperature may be in the range of room temperature to 100° C.

The resulting thiazolidine derivative (I) can be isolated and purified by conventional procedures such as concentration at atmospheric or subatmospheric pressure, solvent extraction, crystallization, recrystallization, phasic transfer, chromatography, etc.

The compound (VII) which is used as the starting material in the above preparation method (1) can be produced, for example, by the steps of diazotizing the corresponding aniline compound and subjecting the diazo-compound to Meerwein arylation.

The following reference and working examples are given to illustrate this invention in further detail.

REFERENCE EXAMPLE 1

In 200 ml of methanol is dissolved 19.0 g of 4-[2-(N,N-dibenylamino)ethoxy]nitrobenzene and after 3 g of 10% Pd-C (50% wet) is added, catalytic reduction is carried out at atmospheric temperature and pressure. The reaction system absorbs about 6.4 l of hydrogen in 75 minutes. The catalyst is then filtered off, the filtrate is concentrated under reduced pressure and the oily residue is dissolved in a mixture of 100 ml methanol and 100 ml acetone. Following the addition of 21.5 ml of concentrated hydrochloric acid, the solution is cooled to 0° C. and a solution of 4.9 g sodium nitrite in 10 ml water is added dropwise at a temperature not exceeding 5° C. The mixture is stirred at 5° C. for 20 minutes, at the end of which time 31.3 g (34.9 ml) of methyl acrylate is added. The reaction mixture is heated to 35° C. and 1 g of cuprous oxide is added in small portions, whereupon the temperature of the reaction system rises to 44° C. with the evolution of nitrogen gas. The mixture is stirred for one hour and after the temperature has dropped to room temperature, it is allowed to stand overnight. The solvent is then distilled off under reduced pressure and the residue is made strongly basic with concentrated aqueous ammonia. Then, following the addition of water, extraction is carried out with ethyl acetate. The extract is washed with water, dried over sodium sulfate and distilled to remove the ethyl acetate. The oily residue is chromatographed on a column of 300 g silica gel, elution being carried out with chloro-hexane (1:9), by the above procedure is obtained 10.7 g (44.8%) of ethyl 2-chloro-3-[4-[2-(N,N-dibenylamino) ethoxy]phenyl] propionate.

IR(liquid film) ν_{max}^{neat}: 2945, 2850, 1745, 1605, 1505, 1250, 1170, 1030

NMR δppm CDCl$_3$: 0.9-1.6(6H, t), 3.2-4.8(8H,m), 2.52(4H,s), 2.85(2H,t), 3.0-3.3(2H,m), 3.3(2H,s), 4.2(2H,s), 6.4(1H,s), 6.75-7.30(4H,q).

EXAMPLE 1

(a) A mixture of 3.6 g of ethyl 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)phenyl]propionate, 0.73 g of thiourea and 3 ml of sulfolane is heated at 120° C. for 4 hours and after cooling, 15 ml of water is added. The oil is separated, ether is added to the oil and the crystalline insolubles (a) are separated from the solution (b) by filtration. The filtrate (b) is distilled to remove the solvent and the residue is run onto a column of 100 g silica gel, elution being carried out with chloroform. By the above procedure is obtained 1.7 g of 5-[4-(2-methyl-2-phenylpropyloxy)benzyl]-thiazolidine-2,4-dione. m.p. 107°-108° C. (benzene-ligroin)

On the other hand, crystals (a) are recrystallized from ethanol-acetone (3:1) to obtain 1 g of 2-imino-5-[4-(2-methyl-2-phenylpropyloxy)benzyl]thiazolidin-4-one with a decomposition point of 210°-213° C. A 300 mg portion of this crystalline product is boiled with 2 ml of sulfolane and 2 ml of 6 N-HCl at 170° C. for 5 hours. After cooling, 50 ml of water is added and the resulting crystals are recrystallized from benzene-ligroin. By the above procedure is obtained 230 mg of 5-[4-(2-methyl-2-phenylpropyloxy) benzyl]thiazolidine-2,4-dione.

EXAMPLE 2

A mixture of 17 g of ethyl 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)phenyl] propionate, 11 g of thiourea and 60 ml of sulfolane is heated at 110° C. for 6 hours and, then, boiled with 10 ml of 2 N-sulfuric acid (or 2 ml of 6 N-HCl) for 16 hours. After cooling, 1 l of water is added and the oil is separated and allowed to stand for a while, whereupon crystals separate out. These crystals are recrystallized from benzene-ligroin. By the above procedure is obtained 19.9 g of 5-[4-(2-methyl-2-phenylpropyloxy) benzyl]thiazolidine-2,4-dione.

EXAMPLE 3

(a) 333 mg of 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy) phenyl]propionic acid and 150 mg of thiourea are heated with 2 ml of sulfolane at 120° C. for 1.5 hours and, following the addition of 2 ml of 6 N-HCl, the mixture is further heated for 5 hours, at the end of which time 10 ml of water is added. The resulting crystals are recovered by filtration. By the above procedure is obtained 340 mg of 5-[4-(2-methyl-2-phenylpropyloxy)benzyl]thiazolidine-2,4-dione.

(b) The same procedure as that described in (a) is repeated except that 355 mg of sodium 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)phenyl]propionate are employed. By this procedure is obtained 330 mg of 5-[4-(2-methyl-2-phenylpropyloxy)benzyl]thiazolidine-2,4-dione.

(c) The same procedure as that described in (a) is repeated except that 332 mg of 2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)phenyl]propionamide is employed. By the procedure is obtained 340 mg of 5-[4-(2-methyl-2-phenylpropyloxy)benzyl]thiazolidine-2,4-dione.

(d) In 10 ml of ethanol are dissolved 1.0 g of amino-2-chloro-3-[4-(2-methyl-2-phenylpropyloxy)-phenyl]propionate and 0.8 g of thiourea and the solution is heated for 5 hours, at the end of which time 50 ml of water is added.

By the above procedure is obtained 1.6 g of 2-imino-5-[4-(2-methyl-2-phenylpropyloxy)benzyl]thiazolidin-4-one.

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SA33

EXAMPLE 4

In 7 ml of dimethylsulfoxide are dissolved 300 mg of 2-bromo-3-[4-(4-chlorobenzyloxy)phenyl]propionic acid and 100 mg of thiourea and the solution is heated at 110° C. for 1 hours. Then, after 0.5 ml of water is added, the solution is further heated for 5 hours. Then, 10 ml of water is added and the resulting crystals are recovered by filtration and recrystallized from benzene-n-hexane (1:1). By the above procedure is obtained 179 mg of 5-[4-(4-chlorobenzyloxy)benzyl]thiazolidine-2,4-dione.

EXAMPLE 5

1.9 g Of ethyl 3-[4-(2-methyl-2-phenylpropyloxy)-phenyl]-3-(benzenesulfonyloxy)-propionate is dissolved in 20 ml of ethanol and to the solution 20 ml of 4 N hydrochloric acid is added. The reaction is refluxed for 24 hours. After cooling, water is added to the reaction mixture is subjected to extraction with ether. The extract is washed with water and then dried. After distilling off ether, the residue is crystallized from ether-n-hexane, whereby 730 mg of 5-[4-(2-methyl-2-phenylpropyloxy)benzyl]thiazolidine-2,4-dione is obtained.

EXAMPLE 6

2.1 g Of ethyl 2-methanesulfonyloxy-3-[4-(1-methyl-2-phenylpropyloxy)phenyl]propionate and 0.76 g of thiourea are added to 10 ml of sulfolane, and the mixture is heated at 110° C. with stirring for one hour. After adding 30 ml of 2 N—hydrochloric acid, the mixture is heated at 100° C. for 8 hours. After cooling, water is added to the mixture, and the mixture is subjected to extraction with ether. The extract is washed with water and dried. The ether is distilled off to give 1.3 g of 5-[4-(2-methyl-2-phenylpropyloxy)benzyl]thiazolidine-2,4-dione.

EXAMPLE 7

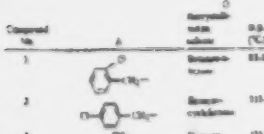
2.0 g Of ethyl 2-methanesulfonyloxy-3-[4-(1-methylcyclohexyloxy)phenyl]propionate and 760 mg of thiourea are added to 30 ml of ethanol. The mixture is refluxed for 2 hours. To the mixture is added 10 ml of hydrochloric acid, and the mixture is further refluxed for 16 hours. After cooling, water is added to the mixture. The mixture is subjected to extraction with ethyl acetate. The extract is washed with water and dried. The ethyl acetate is distilled off to give 1.4 g of 5-[4-(1-methylcyclohexyloxy)benzyl]thiazolidine-2,4-dione. Crystallization from 85% ethanol gives crystals melting at 130°-131° C.

EXAMPLE 8

To 12 ml of dimethylsulfoxide is dissolved 1.12 g of 5-(4-hydroxybenzyl)thiazolidine-2,4-dione, and 480 mg of 50% sodium hydride in oil is added to the solution. The mixture is stirred at room temperature for 15 minutes, to which is added 0.81 g of 4-chlorobenzyl chloride. The whole mixture is stirred at 50° C. for 4 hours. Water is added to the mixture and the mixture is acidified with 2 N - hydrochloric acid. The mixture is subjected to extraction with ether. The extract is washed with water and dried. Ether is distilled off to give an oily substance. The oily substance is subjected to column chromatography on 30 g silica gel, elution being carried out with cyclohexane-ethyl acetate (2:1). By the above procedure there was obtained 423 mg of 5-[4-(4-chlorobenzyloxy)benzyl]thiazolidine-2,4-dione.

EXAMPLE 9

By procedures analogous to those described above in Examples 1 to 4, the following compounds were synthesized.



Compound No.	A	Recrystallization solvent	m.p. (°C.)	Analogous Example No.
1		Benzene-n-hexane	88-89	1,3
2		Benzene-cyclohexane	115-116	3
3		Benzene-ligroin	110-120	1,3
4		Isopropyl ether	128-129	1
5		Ethanol-water	100-104	1,3
6		Cyclohexane	158-160	1

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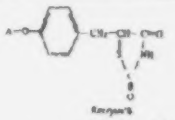
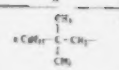
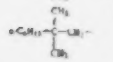
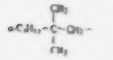
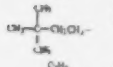
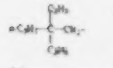
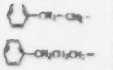
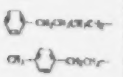
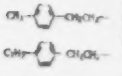
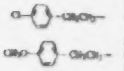
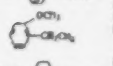
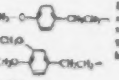
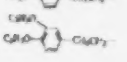
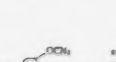
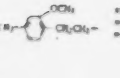
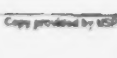


Example No.	R	Recrystallization solvent	m.p. (°C)	Analogous Example No.
7		Cyclohexane	108–110	2
8		Cyclohexane	109–111	2
9		Cyclohexane	107–109	2
10		Ethanol-benzene	106–108	1,2
11		n-Hexane	66–70	2
12		Benzene-ligroin	93–94	1,3
13		Ethyl acetate-cyclohexane	79–80	1
14		Ethyl acetate-cyclohexane	85–87	1
15		Ethyl acetate-cyclohexane	123–124	3
16		Ethanol-water	89–91	3
17		Ethyl acetate	146–148	3
18		Ethyl acetate-benzene	184–187	3
19		Ethanol-benzene	73–77	2
20		Ethyl acetate-n-hexane	103–104	2
21		Ethanol-benzene	110–111	2
22			Oil NMR(cm^{-1}): 3300, 1700, 1700, 1600 Reported Mw	2
23		n-Hexane-benzene	93–95	2

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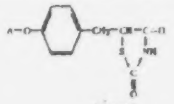
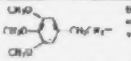
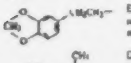
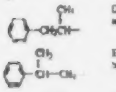
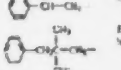
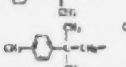
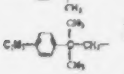
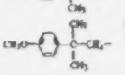
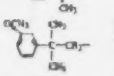
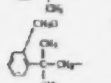
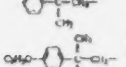
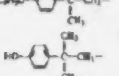
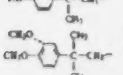
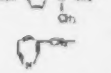
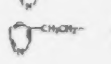


Compound No.	A	Recrystallization solvent	m.p. (°C)	Analogous Example No(s)
21		Ethyl acetate-ether	108.5-109.5	1
22		Ethyl acetate-ether	132-133	1
23		Chloroform	84-85	1
24		Chloroform	66-67	1,3
25		Chloroform	182-184	1
26		Cyclohexane	106-107	1
27		Ethanol	104-120	1
28		Ethanol	109-120	1
29		Ethanol	65-69	1
30		Ethanol	116-117	1
31		Ethanol	77-80	1
32		Ether	137-138	3
33		Ethanol	120-122	1
34		Methanol	101-104	1
35		Chloroform-methanol	175-176	1,3

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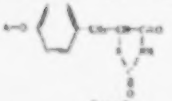

Compound No.	A	Recrystallisation solvent	m.p. (°C.)	Analogous Example No.
47		Chloroform/diethyl ether	128-131	1
48		[illegible]	209-210	1,3
49		Methanol	167-168	1
50		Ethyl acetate/diethyl ether	152-154	1
51		Ethanol/water	161-163	1
52		Ethanol	155-156.5	1
53		Cyclohexane	93-95	1
54		n-Pentane	120-122	1,3
55		Benzene/hexane	137-138	1,3
56		Cyclohexane	124-126	1,3
57		Ligroin	88-90	1
58		n-Hexane	85-87	1
59		Benzene/hexane	98-100	1
60		Ether/n-hexane	88-89	3
61		Ether/n-hexane	103-104	2

EXAMPLE 10

A mixture of 10.1 g. methyl 2-chloro-3-[4-(2-methoxyethoxy)phenyl]propionate and 6.64 g. thiourea is heated in the presence of 100 ml. of methanol at 120° C. for 4 hours. After cooling, a saturated aqueous solution of sodium hydrogen carbonate is added and the mixture is extracted with ethyl acetate. The extract is washed with water, dried over sodium sulfate and distilled to remove the ethyl acetate, whereupon 6.1 g. (60.7%) of 2-amino-5-[4-(2-methoxyethoxy)benzyl]thiazolin-4-one is obtained as crystals. These crystals are recrystallized from ethyl acetate-methanol. Colorless needles, m.p. 159°-160° C.

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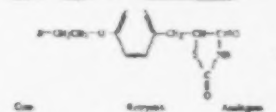
In 50 ml of 1 N - HCl is dissolved 4.1 g of the above 2-amino 5-[4-(2-morpholinoethyloxy)benzyl]thiazolidin-4-one and the solution is heated under reflux for 16 hours. After cooling, the reaction mixture is neutralized with a saturated aqueous solution of sodium hydrogen carbonate and extracted with ethyl acetate. The extract is washed with water, dried over sodium sulfate and distilled to remove the ethyl acetate, whereupon 3.1 g (61.7%) of 3-[4-(2-morpholinoethyloxy)benzyl]thiazolidine-2,4-dione is obtained as crystals. These crystals are recrystallized from dimethylformamide-water. Colorless prisms, m.p. 189°–189° C.

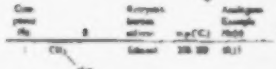
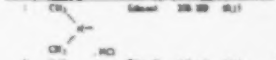
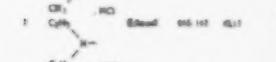
EXAMPLE 11

A mixture of 9.9 g methyl 2-chloro-3-[4-[2-(N,N-dimethylamino)ethyloxy]phenyl]propionate and 2.4 g thiourea is heated on the process of 100 ml of n-butanol at 100° C. for 15 hours. After cooling, the n-butanol is fractional off under reduced pressure, 100 ml of 2 N - HCl is added to the residue and the mixture is heated at 100° C. for 6 hours. After cooling, the reaction mixture is neutralized with a saturated aqueous solution of sodium hydrogen carbonate and extracted with ethyl acetate. The extract is washed with water, dried over $MgSO_4$ and distilled to remove the ethyl acetate, whereupon 6.0 g (69.2%) of 5-[4-[2-(N,N-dimethylamino)ethyloxy]benzyl]thiazolidine-2,4-dione is obtained as crystals. These crystals are recrystallized from ethanol. Colorless prisms, m.p. 134°–135° C.

EXAMPLE 12

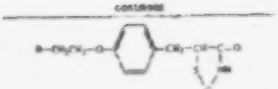
By procedures analogous to those described in Example 10 or 11, the following compounds were synthesized.



Compound No.	R	Recrystallization solvent	m.p. (°C.)	Analogous Example No.
1	CH_3 	Ethanol	208–209	10,11
2	C_2H_5 	Ethanol	195–197	10,11
3	n-C_3H_7 	Ethanol	229–231	11
4	n-C_4H_9	Ethanol	230–232	11
5	n-C_5H_{11}	Ethanol	98–99	10,11
6	n-C_6H_{13}	Methanol	202–204	11

HCl

continued



Compound No.	R	Recrystallization solvent	m.p. (°C.)	Analogous Example No.
7		Methanol	240–242	11

HCl

EXAMPLE 13

An example of practical recipe in which the compound of the invention is utilized as remedies for diabetes is as follows.

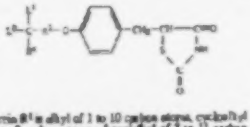
(Table)

(i)	Subject: carbon tetrachloride
	Particulate hydroxypropyl methylcellulose 2910 (Shin-Etsu Chemical Co., Ltd.)
	Lactose
	Corn starch
	Microcrystalline cellulose
	Magnesium stearate
	100 mg

(1), (2), (3) and 1 quantity of (4) are thoroughly mixed, and then the mixture is granulated. Remaining 1 quantity of (4), and (5) are added to the granules and compressed into tablets. Thus prepared tablets can be further coated with a suitable coating agent.

What is claimed is:

1. A thiazolidine derivative of the general formula



wherein R^1 is alkyl of 1 to 10 carbon atoms, cycloalkyl of 3 to 7 carbon atoms, phenylalkyl of 7 to 11 carbon atoms, or phenyl; R^2 means a bond or a lower alkylene group; L^1 and L^2 are the same or different and each a lower alkyl or L^1 and L^2 are combined to form an alkylene group, provided that when R^1 is other than alkyl, L^1 and L^2 may further be hydrogen.

2. A thiazolidine derivative as claimed in claim 1, wherein R^1 is an alkyl having 1 to 10 carbon atoms.

3. A thiazolidine derivative as claimed in claim 1, wherein L^1 and L^2 are combined to form an alkylene group having 2 to 6 carbon atoms.

4. A thiazolidine derivative as claimed in claim 1, wherein R^2 is a lower alkylene group having 1 to 3 carbon atoms.

5. A thiazolidine derivative as claimed in claim 1, wherein R^1 is an alkyl having 1 to 10 carbon atoms, L^1 and L^2 are combined to form an alkylene group having 2 to 6 carbon atoms, and R^2 is a lower alkylene group having 1 to 3 carbon atoms.

6. A thiazolidine derivative as claimed in claim 1, wherein the derivative is 5-[4-(1-methylcyclohexylmethyloxy)benzyl]thiazolidine-2,4-dione.

7. A hypoglycemic and hypoglycemic pharmaceutical composition, which comprises, as active ingredient, the effective amount of a thiazolidine derivative defined in claim 1.

8. A hypoglycemic and hypoglycemic pharmaceutical composition as claimed in claim 1, wherein the derivative is 5-[4-(1-methylcyclohexylmethyloxy)benzyl]thiazolidine-2,4-dione.

* * * * *

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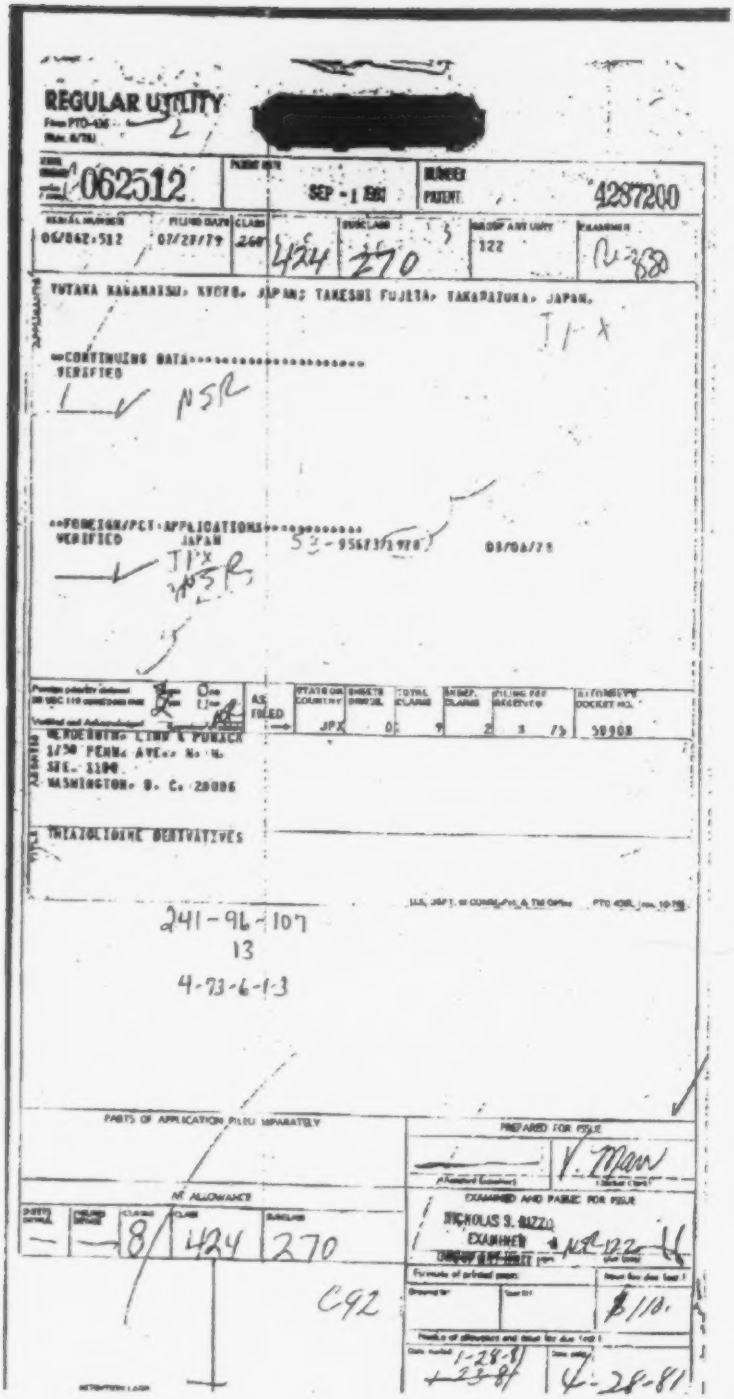

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YUTAKA NAKANAISHI, KYOTO, JAPAN; TAKESHI FUJITA, TAKARAZUKA, JAPAN.

CONTINUING DATA

VERIFIED

FOREIGN/PCT APPLICATIONS

VERIFIED JAPAN 53-95873/1978 08/08/78

AS FILED | STATE OR COUNTRY JPX | SHEETS DRAWING 01 | TOTAL CLAIMS 9 | INDEP. CLAIMS 2 | FILING FEE RECEIVED 3 75 | ATTORNEY'S DOCKET NO. 50908

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THIAZOLIDINE DERIVATIVES

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4-73-6-1-3

PARTS OF APPLICATION FILED SEPARATELY

PREPARED FOR ISSUE

AT ALLOWANCE

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EXAMINED AND PASSED FOR ISSUE

NICHOLAS S. RIZZO
EXAMINER

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4-28-81

SA39

MAIL ROOM MAY 29 1980 U.S. PATENT AND TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of :

YUTAKA KAWAMATSU et al :

Serial No. 52,512 : Group Art Unit 122

Filed July 27, 1979 :

Thiazolidine Derivatives:

RECEIVED JUN 9 1980 GROUP 122

DECLARATION UNDER RULE 132

I, Takeshi Fujita, a citizen of Japan residing at 13-15, Nagaodai 1-chome, Takarazuka, Hyogo, Japan, sincerely declare;

That I was born on May 1, 1937 in Japan;

That I graduated from Faculty of Liberal Arts and Science, Shizuoka University in March, 1960;

That I received Master of Science degree for Biochemistry, from the Institute for Protein Research, Osaka University in March, 1962;

That I received Ph. D. degree for "Biochemical Studies on Bacterial Cytochromes", from the Institute for Protein Research, Osaka University in March, 1965;

That I have been an employee of Biological Research Laboratories, Takeda Chemical Industries, Ltd., Osaka, Japan since April, 1965;

That I have engaged in the field of Biochemistry and Drug Metabolism in the laboratory of the said company;

That I have been Head of Biochemistry, Biological Research Laboratories since February, 1975;

That I have been a member of the Japanese Biochemical Society since 1960;

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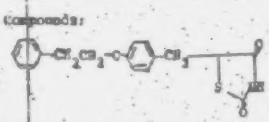
SA40

That the following experiments were carried out by my assistants under my direct guidance and supervision.

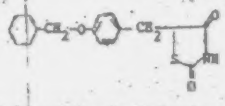
Experiment

Tests for blood glucose and lipid lowering effects

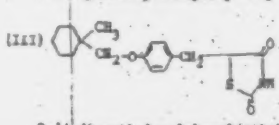
(1) Test Compounds:

(I) 

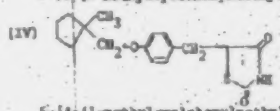
5-[4-(2-phenylethyloxy)benzyl]thiazolidine-2,4-dione

(II) 

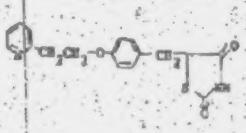
5-[4-cyclohexylmethyloxybenzyl]thiazolidine-2,4-dione

(III) 

5-[4-(1-methylcyclohexylmethyloxy)benzyl]thiazolidine-2,4-dione

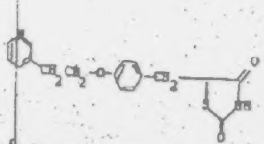
(IV) 

5-[4-(1-methylcyclohexylmethyloxy)benzyl]thiazolidine-2,4-dione

(V) 

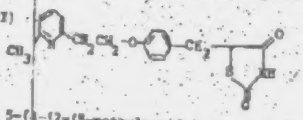
5-[4-[2-(2-pyridylethyloxy)]benzyl]thiazolidine-2,4-dione

(VI)



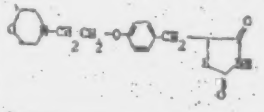
5-[4-[2-(3-pyridylethyloxy]benzyl)thiazolidine-2,4-dione

(VII)



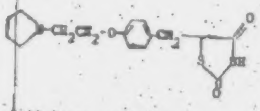
5-[4-[2-(5-methylpyrid-2-yl ethyloxy)]benzyl]thiazolidine-2,4-dione

(VIII)



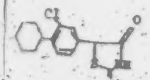
5-[4-(2-morpholinoethyloxy)benzyl]thiazolidine-2,4-dione

(IX)



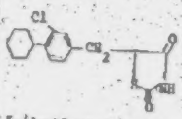
5-[4-[2-(1-pyrrolidinyl]ethyloxy]benzyl)thiazolidine-2,4-dione

(I)

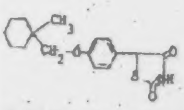


5-[3-chloro-4-cyclohexylphenyl)thiazolidine-2,4-dione

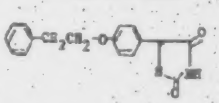
(II)



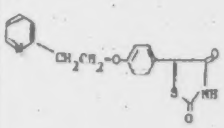
5-[3-chloro-4-cyclohexylbenzyl]thiazolidine-2,4-dione

(iii) 

5-[4-(1-methylcyclohexylmethyloxy)phenyl] thiazolidine-2,4-dione

(iv) 

5-[4-(2-phenylethyloxy)phanyl]thiazolidine-2,4-dione

(v) 

5-{4-[2-(2-pyridylethyloxy)]phenyl}thiazolidine-2,4-dione

(2) Animals employed in the tests:

Male genetically obese and diabetic mice, yellow KK, 8 to 10 weeks old.

(3) Test method:

The compounds to be tested were added to the powdered laboratory chow at levels shown in Table 1, and given to the mice for 4 days with free access to water. Blood samples were taken from the orbital vein. Fed blood glucose and plasma triglycerids were determined by the method of glucose oxidase and Fletcher, respectively.

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(4) Result:

The results are shown in the following Table I.

Table I

Compounds	Dose (% in diet)	Blood Glucose ①	Plasma Triglyceride ①
I	0.02	29 *	27 *
II	0.02	38 ***	56 ****
III	0.07	45 ***	45 ***
IV	0.02	52 ****	47 ***
V	0.02	50 ***	47 ***
VI	0.02	51 ****	43 **
VII	0.02	50 ***	48 ****
VIII	0.02	52 ***	37 ***
IX	0.02	53 ***	37 ***
i	0.05	0	-21
ii	0.05	-1	-6
iii	0.1	-2	-91
iv	0.1	7	-21
v	0.05	-2	-6

(Note) Significant difference was ascertained with Student's t-test

*: $P<0.05$; **: $P<0.02$, ***: $P<0.01$, ****: $P<0.001$ VS control

①: % reduction from the control.

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It is declared by the undersigned that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Signed this 8 th day of May, 1980.

Takeshi Fujita

Takeshi Fujita

SA45

(Chem. Pharm. Bull.)

Studies on Antidiabetic Agents. II.[1] Synthesis of 5-[4-(1-Methylcyclohexylmethoxy)benzyl]thiazolidine-2,4-dione (ADD-3878) and Its Derivatives

TAKASHI SOHDA, KATSUTOSHI MIZUNO, KIKO IMAMIYA, YASUO SUGIYAMA, TAKESHI FUJITA, and YUTAKA KAWAMATSU*

Central Research Division, Takeda Chemical Industries, Ltd., 17-85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532, Japan

(Received April 22, 1982)

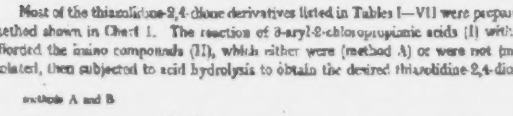
More than 100 5-substituted thiazolidine-2,4-diones were prepared and their hypoglycemic and hypolipidemic activities were evaluated with genetically obese and diabetic rats, yellow KK. The structure-activity relationship study showed that the 5-[4-oxybenzyl] moiety is essential for substantial activity. Among these compounds, 5-[4-(cyclohexylmethoxy)benzyl]thiazolidine-2,4-dione (47), 5-[4-(1-methylcyclohexylmethoxy)benzyl]-thiazolidine-2,4-dione (49, ADD-3878) and 5-[4-(2-(5-pyridyl)ethoxy)benzyl]thiazolidine-2,4-dione (59) exhibited the most favorable properties in terms of activity and toxicity.

Keywords—5-benzylthiazolidine-2,4-dione; hypoglycemic activity; hypolipidemic activity; genetically obese and diabetic rats (yellow KK); structure-activity relationship

In the preceding paper,[1] we reported that 5-[4-(2-methyl-2-phenylpropoxy)benzyl]-thiazolidine-2,4-dione (1, AL-321), prepared from ethyl 2-chloro-3-[4-(2-methyl-2-phenylpropoxy)phenyl]propionate by reaction with thiourea followed by acid hydrolysis, had potent hypoglycemic and hypolipidemic activities. The present paper reports chemical modifications of the substituents at the 5-position of the thiazolidine ring in 1 and their effects on the pharmacological activities. 5-Benzylthiazolidine-2,4-diones bearing the 4-oxy group in the benzyl moiety, *i.e.*, 1—73, were prepared to investigate the structure-activity relationships. The synthesis and activities of 5-[4-aminobenzyl]- and 5-[2-alkoxy-5-pyridylmethyl]thiazolidine-2,4-dione derivatives, i.e., 74—83 and 92—101, respectively, are also described.

Chemistry

Most of the thiazolidine-2,4-dione derivatives listed in Tables I—VII were prepared by the method shown in Chart 1. The reaction of 3-aryl-2-chloropropionic acids (I) with thiourea afforded the imino compounds (II), which either were (method A) or were not (method B) isolated, then subjected to acid hydrolysis to obtain the desired thiazolidine-2,4-diones (III).



Ar = substituted phenyl, 2-alkoxy-5-pyridyl

Chart 1

Although the 3-aryl-2-chloropropionic acid derivatives (I) used in this reaction include esters, amides and sodium or ammonium salts as well as the free acids, the methyl or ethyl esters were mainly used in this study. Compounds III were also prepared by the methods shown in Chart 2 (methods C and D).[1,2]

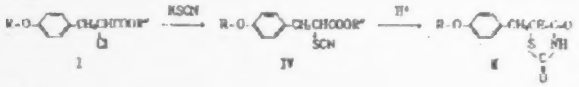


Chart 3

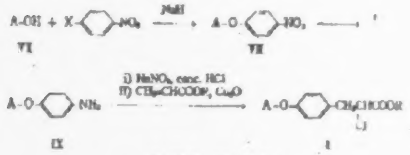


Chart 5

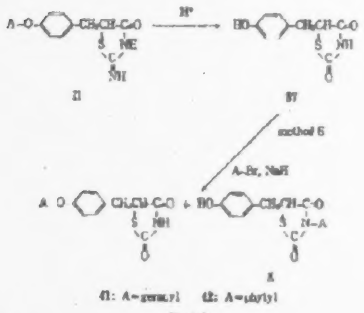


Chart 6

The starting compounds (I) with 4-oxy substituents were prepared by the general process shown in Chart 3, which includes the Meerwein arylation reaction (i.e., IX→I), as described previously.[1,2]

As shown in Chart 6, acid hydrolysis of the imino compound (II) bearing a geranyloxy or phytyloxy group resulted in concomitant cleavage of the ether linkage to yield a phenolic compound 87 (Table VI). Compounds 41 and 42 (Table III) were therefore prepared by *O*-alkylation of 87 (method E). In this method, the *N*-alkylated compound (X) was isolated as a by-product (Chart 6).

SA47

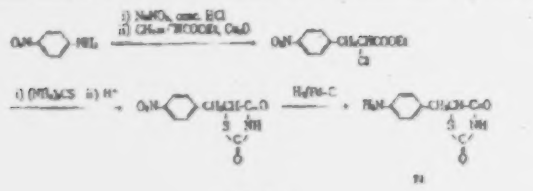


Chart 5

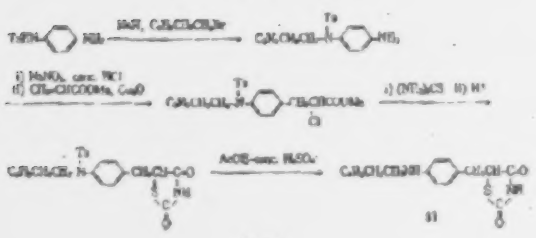


Chart 6

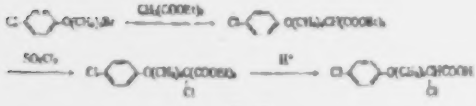


Chart 7

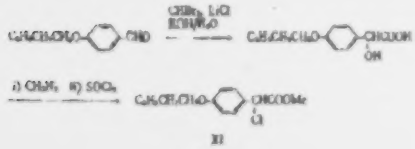


Chart 8

Compound 64 (Table IV) was prepared by concomitant hydrolysis of the 2-imino group on the thiazolidine ring and the *N*-benzoyl group on the pyrrolidine ring of the corresponding imino compound (II) (method *b*).

A series of compounds listed in Table V (except 81) was prepared from 74, which was derived starting from *p*-nitroaniline as shown in Chart 6.

Appropriate acylation of 74 gave the corresponding 6-(4-acylaminobenzyl)thiazolidine-2,4-diones (76, 77 and 87). Reaction of 74 with *p*-toluenesulfonyl chloride, ethoxycarbonylmethylenecyanate and bis(2-chloroethyl)amine afforded 75, 80 and 83, respectively. Conden-

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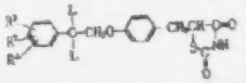
(R)$_n$ = 4-(CH$_3$)$_3$CCO-, 3,4-(CH$_3$O)$_2$-, 2,4,5-(C$_2$H$_5$O)$_3$-
R' = H, D
X = Cl, Br

Cont'd

TABLE 1. Physical and Biological Properties of Thiazolidine-2,4-dione Derivatives



No.	L	R^1	R^2	R^3	Method[a]	Yield[b] (%)	mp (°C)	Recrysta. solvent[c]	Formula[d]	Hypo glycemic activity[e]	Plasma triglyceride cholesterol-lowering activity[e]
1 (AL-321)	CH$_2$	H	H	H	A	88.7	110—111	Et-W	$C_{18}H_{17}NO_3S$	3	3
					B	89.6					
					C	72.5					
					D	78.4					
2	CH$_2$	4-CH$_3$	H	H	B	66.3	110—111	E-H	$C_{19}H_{19}NO_3S$	2	2
3	CH$_2$	2-CH$_3$O	H	H	B	77.6	116—117	E-H	$C_{19}H_{19}NO_4S$	3	3
4	CH$_2$	3-CH$_3$O	H	H	B	81.4	68—69	D-H	$C_{19}H_{19}NO_4S$	3	2
5	CH$_2$	4-CH$_3$O	H	H	B	58.1	107—108	E-E	$C_{19}H_{19}NO_4S$	1	2
6	CH$_2$	4-C$_2$H$_5$	H	H	B	85.7	104—105	D-H	$C_{20}H_{21}NO_3S$	3	1
7	CH$_2$	4-C$_3$H$_7$O	H	H	B	81.7	92—93	P-H	$C_{21}H_{23}NO_4S$	3	3
8	CH$_2$	4-OH	H	H	B	67.2	157—158	E	$C_{18}H_{17}NO_4S$	3	3
9	CH$_2$	3-CH$_3$O	4-CH$_3$O	H	B	80.4	106—107	E-H	$C_{20}H_{21}NO_5S$	3?	1?
10	H	H	H	H	B	69.2	93—94	B-E	$C_{17}H_{15}NO_3S$	3	4
11	H	4-CH$_3$	H	H	B	77.8	120—121	EA-H	$C_{18}H_{17}NO_3S$	3	2
12	H	3-CH$_3$O	H	H	B	89.3	73—75	A-H	$C_{18}H_{17}NO_4S$	3	4
13	H	4-CH$_3$O	H	H	B	71.0	104—105	EA-H	$C_{18}H_{17}NO_4S$	3	3
14	H	4-C$_2$H$_5$	H	H	B	78.5	87—88	E-H	$C_{19}H_{19}NO_3S$	3	2
15	H	4-C$_3$H$_7$O	H	H	B	79.5	102—103	EA-H	$C_{21}H_{23}NO_4S$	3	4
16	H	4-Cl	H	H	B	87.7	148—149	EA	$C_{17}H_{14}ClNO_3S$	3	3
17	H	3-CH$_3$O	4-CH$_3$	H	B	75.9	88—90	EA-H	$C_{19}H_{19}NO_4S$	3	3
18	H	3-CH$_3$O	4-CH$_3$O	H	B	70.0	110—111	EA-E	$C_{19}H_{19}NO_5S$	3	4
19	H	3-CH$_3$O	4-CH$_3$O	5-CH$_3$O	B	43.9	109—110	EA-H	$C_{20}H_{21}NO_6S$	3	2
20	H	3,4-OCH$_2$O		H	B	73.1	132—133	EA-H	$C_{18}H_{15}NO_5S$	3	3

a) See "Experimental".

b) Overall yield from the corresponding 3-haloketone (Ia: 1-one (II), [and ref. 4]), 3-chloro-4-oxybutanoate ester (R) (method B), 3 and 5 chloroacetophenone (IV) (method C) or 4-bromo-5-oxypentanoate (V) (method D).

c) A=acetone, B=C$_2$H$_5$, C=CHCl$_3$, Cy=cyclohexane, E=ETOH, H=hexane, D=diisopropyl ether, L=ligroin, M=MeOH, P=petroleum ether, Pr=propanol, W=H$_2$O.

d) All compounds were analyzed for C, H and N, and their results obtained for these elements were within ±0.4% of the calculated values.

e) Maximum reductions in blood glucose and plasma triglyceride levels at the dosage of 5 mg/kg/day in the diet were calculated as percentage with respect to the control value; 70—80%, reduction=3, 50—69%, reduction=2, 30—49%, reduction=1, 30—
0%, reduction=0, 30—99%, reduction=-1, less than 9%, reduction=-2

f) The dosage 5 mg/kg/day

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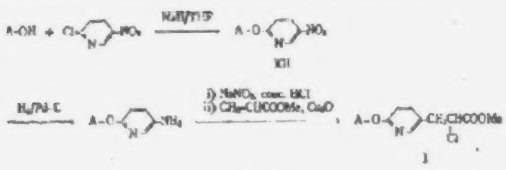
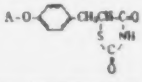


Chart 10

TABLE II. Physical and Biological Properties of Thiazolidine-2,4-dione Derivatives



No.	A	Method[c]	Yield[d] (%)	mp (°C)	Recrystn. solvent[e]	Formula[f]	Hypoglycemic activity[g]	Plasma triglyceride-lowering activity[g]
31	C_6H_5-	B	93.4	119—119	B-H	$C_9H_9NO_2S$	1	1
10	$C_6H_5(CH_2)_2CH_2$-						3	4
32	$C_6H_5CH_2CH_2CH_2$-	B	48.9	79—80	EA-Cy	$C_{12}H_{13}NO_2S$	2	1
		C	75.6					
33	$C_6H_5CH_2CH(CH_3)CH_2$-	B	36.4	83—83	EA-Cy	$C_{13}H_{15}NO_2S$	2	1
34	$C_6H_5CH(CH_3)CH_2$-	B	78.5	Oil[h]	—	$C_{12}H_{13}NO_2S$	3	2
35	$C_6H_5CH_2CH(CH_3)$-	B	78.7	84—85	E-H	$C_{12}H_{13}NO_2S$	3	3
1	$C_6H_5(CH_2)_3CH_2$- (AL-321)						3	3
36	$C_6H_5CH_2C(CH_3)_2CH_2$-	B	85.8	107—108	EA-H	$C_{13}H_{15}NO_2S$	3	2
		C	71.1					
37	$(C_6H_5)_2CHCH_2$-	B	77.9	163—163	Et	$C_{18}H_{17}NO_2S$	1	1
38	$(C_6H_5)_2C(CH_3)CH_2$-	B	80.8	Oil[h]	—	$C_{19}H_{19}NO_2S$	2	3
39		B	91.0	126—127	D-E	$C_{16}H_{19}NO_3S$	5	1
40	3-Cl-C_6H_4-	D	44.6	89—90	EA-H	$C_{15}H_{10}ClNO_2S$	2	1
41	4-Cl-$C_6H_4CH_2$-	B	64.7	135—136	B-Cy	$C_{17}H_{14}ClNO_2S$	2	2
42	2-Cl-C_6H_4-CH_2-	B	93.0	85—86	D-H	$C_{17}H_{14}ClNO_2S$	3	2
43	3,4-$(OCH_2)_2$-$C_6H_3CH_2$-	B	44.9	178—177	C	$C_{13}H_{13}NO_4S$	1	1

a—c) See the corresponding footnotes in Table I.
f) Purified by silicone chromatography.

sation of 74 with *N*-protected ω-aminoalkanoic acids by the mixed anhydride method followed by deprotection yielded 78 and 79 (see "Experimental"). Compound 81 was prepared by the method illustrated in Chart 6.

2-Chloro-6-(4-chlorophenoxy)hexanoic acid required for the preparation of 84 was prepared by the method illustrated in Chart 7.

Methyl 2-chloro-2-(4-phenethyloxyphenyl)acetate (XI) required for the preparation of 85 (Table VI) was obtained from the corresponding aldehyde as shown in Chart 8.[6]

The starting 3-aryl-2-chloropropionic acids (I) for the preparations of 86 to 88 and 89 to 91 were obtained by the above-mentioned Meerwein arylation reaction of the corresponding aniline derivatives and the method shown in Chart 9, respectively.

A series of 5-(2-substituted-5-pyridylmethyl)thiazolidine-2,4-dione derivatives (92—101)

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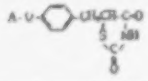
listed in Table VII was prepared by method B, and the starting 5 (5-alkoxy-6-pyridyl)-2-chlorocarboxylic acids (I) were prepared according to the route shown in Chart 10 using 2-chloro-6-nitropyridine.

Biological Method

Genetically obese and diabetic mice, yellow KK^{Ay} (male, 9 weeks old), were used. After prefeeding on a laboratory chow (CE-2, CLEA Japan) for 5 d, they were allocated to experimental groups of five mice each, so that the average blood glucose of each group was the same. The test compounds at 0.1% or 0.05% concentration, were mixed thoroughly with the powdered

Table III. Physical and Biological Properties of 5-(Substituted-benzyl)-2,4-dione Derivatives



No.	A	Method[a]	Yield[b] (%)	mp (°C)	Recrystn. solvent[c]	Formula[d]	Hypoglycemic activity[e]	Fibrinogen uptake inhibitory activity[f]
34	$CH_3(CH_2)_4CH_2-$	B	51.3	58—66	EA–H	$C_{19}H_{29}NO_3S$	1	1
35	$(CH_3)_2CHCH_2-$	B	64.0	95—98	EA–H	$C_{18}H_{27}NO_3S$	1	1
36	$(CH_3)_3CCH_2-$	B	68.0	105—110	E–H	$C_{18}H_{27}NO_3S$	2	3
		C	73.5					
37	$ClCH_2CH_2CH(CH_3)CH_2-$	B	75.1	130—139	IPE	$C_{18}H_{26}ClNO_3S$	3	3
38	$CH_3(CH_2)_4CH(CH_3)CH_2-$	B	56.7	102—106	E–H	$C_{20}H_{31}NO_3S$	3	2
39	$CH_3CH_2CH(CH_3)CH_2-$	B	72.9	102—110	Cy	$C_{18}H_{27}NO_3S$	3	2
40	$CH_3(CH_2)_3CH(CH_3)CH_2-$	B	60.3	101—102	Cy	$C_{19}H_{29}NO_3S$	3	3
41	Geranyl-	B	30.0[g]	95—98	Cy–H	$C_{20}H_{29}NO_3S$	1	0
42	Phytyl-	B	49.9[g]	71—85	H	$C_{30}H_{49}NO_3S$	0	1
43	$CH_3CH=CH(CH_2)_3CH(CH_3)CH_2-$	B	75.6	98—100	Cy	$C_{20}H_{29}NO_3S$	2	0
44	Geranyl-$CH_2CH(CH_3)CH_2-$	B	78.4	Oil[h]	—	$C_{25}H_{41}NO_3S$	1	0
45		B	55.4	86—87	E–H	$C_{19}H_{23}NO_3S$	3	1
46		A	89.9	160—161	Eb–W	$C_{18}H_{21}NO_3S$	1[i]	1[i]
		D	77.5					
47		A	87.3	120—121	Py	$C_{19}H_{23}NO_3S$	2	3
48		D	67.1	62—67	Cy	$C_{20}H_{25}NO_3S$	3	2
49	(AHR-3010)	A	88.3	130—131	El	$C_{19}H_{23}NO_3S$	3	2
		B	87.3					
		C	78.2					
		D	90.9					
50		A	78.9	86—89	H	$C_{20}H_{25}NO_3S$	2	1
51		A	90.4	Oil[h]	—	$C_{20}H_{25}NO_3S$	3	3
52		A	80.2	127—128	B–L	$C_{19}H_{23}NO_3S$	3	3
53	Benzoyl-	A	69.5	153—154	Eb–W	$C_{19}H_{21}NO_4S$	2	2
54	Benzyl-	A	71.3	146—148	L	$C_{19}H_{23}NO_3S$	0	1
55	4-Methoxybenzyl-	A	87.4	93—98	H	$C_{20}H_{25}NO_4S$	1	1

a—c) See the corresponding footnotes in Table I. d) Unless noted otherwise, analyzed for C, H, N and/or S within ±0.4%. e) Determined by solvent chromatography. f) Test dosage 0.05% (w/w).

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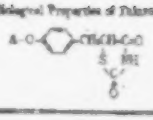
TABLE IV. Physical and Biological Properties of Thiazolidine-2,4-dione Derivatives



No.	A	Method[a]	Yield[b] (%)	mp (°C)	Recryst. solvent[c]	Formula[d]	Hypoglycemic activity[e]	Plasma triglyceride-lowering activity[f]
58		D	69.6	183—186	C-M	$C_{16}H_{14}N_2O_3S$	3	3
59		B	78.4	209—210	DMF-W	$C_{17}H_{16}N_2O_3S$	3	2
60		B	62.7	160—164	EA-H	$C_{18}H_{18}N_2O_4S$ ·1/2H$_2$O	3	1
61		B	61.6	178—179	C-M	$C_{17}H_{16}N_2O_3S$	3*	2*
62		B	77.8	178—177	C-M	$C_{18}H_{18}N_2O_3S$	3	2
63		B	54.3	79—91	E-H	$C_{14}H_{14}NO_3S_2$	3	2
64		B	38.5	60—64	E-H	$C_{14}H_{13}NO_4S$	2	2
65		D	45.0	182—184	Th	$C_{14}H_{14}N_2O_3S_2$	2	3
66		F	33.3*	163—166	E-A	$C_{16}H_{18}N_2O_3S$·HCl	3	1
67	$(CH_3)_2CHNH$-CH_2CH_2-	D	62.9	228—231	M-E	$C_{16}H_{20}N_2O_3S$·HCl	1	1
68	$(CH_3)_2CHN$-CH_2CH_2-	B	57.9	205—211	E1	$C_{17}H_{22}N_2O_3S$·HCl	1	1
69	$C_6H_5CH_2N$-CH_2CH_2-	D	64.3	131—132	A-E	$C_{20}H_{20}N_2O_3S$·HCl	2	1
70	$C_6H_5CH_2N$-CH_2CH_2-	B	81.5	154—155	E	$C_{20}H_{20}N_2O_3S$	1	-
71	Bu-$C_6H_4CH_2N$-CH_2CH_2-	D	69.2	134—135	H	$C_{24}H_{28}N_2O_3S$	1*	2*
72		A	62.7	188—189	DMF-W	$C_{18}H_{16}N_2O_3S$	3*	2*
73		D	51.3	275—277	F1-W	$C_{17}H_{15}N_3O_3S$·2HCl·1/2H$_2$O	1	1
74		B	58.2	232—234	M	$C_{18}H_{17}NO_3S$·HCl	3	3
75		B	60.5	244—245	M	$C_{19}H_{19}NO_3S$·HCl	3	4

a—c) See the corresponding footnotes to Table I.

f) Ouabain used from acetate 1-(4-O-benzoyl-3-cyclohexylamino-2-propyl)-3-nitroguanidine (Table I).

g) The dosage 0.05% (w/w).

CE-2 diet. The mice were fed the experimental diet and water *ad libitum* for 4 d. Blood samples were taken from orbital vein. Blood glucose and plasma triglyceride were determined by the glucose oxidase method[10] and the method of Fletcher,[9] respectively. The maximum decreases of blood glucose and plasma triglyceride levels were calculated as percentage change from the control value.

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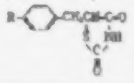
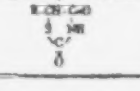
Table V. Physical and Biological Properties of Thiazolidine-2,4-dione Derivatives



No.	R	Yield[a] (%)	mp (°C)	Recrystn. solvent[b]	Formula[c]	Hypoglycemic activity[d]	Plasma triglyceride lowering activity[e]
74	H_2N-	88.9[f]	165—168	M	$C_{11}H_{10}N_2O_3S$	2	1
75	CH_3-(p-)-SO_2NH-	58.6	224—225	M	$C_{17}H_{16}N_2O_5S_2$	2	1
76	CH_3CH_2CONH-	95.8	148—151	EA	$C_{13}H_{14}N_2O_3S$	2	1
77	2-pyridyl-$CONH$-	36.8	271—272	DMF-W	$C_{15}H_{11}N_3O_3S$	1	1
78	$H_2NCH_2CH_2CONH$-	44.8	243—245	M	$C_{13}H_{15}N_3O_3S$·HBr	0	0
79	$H_2N(CH_2)_4CONH$-	47.0	216—218	DMF-E	$C_{15}H_{19}N_3O_3S$	0	0
80	$C_6H_5OCOCH_2NHCONH$-	58.7	161—162	H	$C_{18}H_{15}N_3O_5S$	0	0
81	$C_6H_5CH_2CH_2NH$-	63.4	156—157	A	$C_{18}H_{18}N_2O_3S$·HCl	1	1
82	Cl-(p-)-OCH_2-(m-)-$CONH_2$	98.4	221—222	M	$C_{18}H_{15}ClN_2O_4S$	2	0
83	HN(1)-R-	6.3	222—223	M	$C_{14}H_{14}N_2O_3S$·1/2H_2O	0	0

a) Yield from 76.
b—d) See footnotes (f, d) and e in Table 1, respectively.
e) Yield from 5-[p-(2-ethoxycarbonylethoxy)benzylidene]-2,4-dione.

Table VI. Physical and Biological Properties of Thiazolidine-2,4-dione Derivatives



No.	R	Method[a]	Yield[b] (%)	mp (°C)	Recrystn. solvent[b]	Formula[c]	Hypoglycemic activity[d]	Plasma triglyceride lowering activity[e]
84	Cl-(p-)-$O(CH_2)_3$-		68.7[f]	95—96	EA-H	$C_{18}H_{16}ClNO_3S$	1	0
85	CH_3CH_2O-(p-)-		58.6[g]	119—120	EA-H	$C_{12}H_{13}NO_3S$	0	0
86	Cl-(p-)-CH_2-	B	38.5	130—131	E-H	$C_{10}H_8ClNO_2S$	0	0
87	HO-(p-)-CH_2-	B	60.7	159—160	EA-H	$C_{10}H_9NO_3S$	0	0
88	OCH_2-(p-)-CH_2-	B	47.5	133—134	EA-H	$C_{17}H_{13}NO_3S$	1	2
89	$(CH_3)_3CCO$-(p-)-CH_2-	B	64.6	175—174	Et	$C_{14}H_{17}NO_3S$	2	0
90	CH_3O-(3,4-)-CH_2- (CH_3O)	B	80.4	152—154	M	$C_{12}H_{13}NO_4S$	1	1
91	C_2H_5O-(3-)-OC_2H_5-(4-)-CH_2- (C_2H_5O)	B	81.4	108—106	EA-H	$C_{14}H_{17}NO_4S$	0	0

a—c) See the corresponding footnotes in Table 7.
f) Yield from 5-chloro-3-[4-(4-chlorophenoxybutoxy)benzylidene]-2,4-dione and.
g) Yield from methyl 5-(4-hydroxy-3-[5-ethoxy-2,4-dioxothiazolidin-5-ylmethyl]benzoate (XI).

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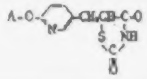
Table VII. Physical and Biological Properties of Thiazolidine-2,4-dione Derivatives



No.	A	Yield[a] (%)	mp (°C)	Recrystn. solvent[b]	Formula[c]	Hypoglycemic activity[d]	Plasma triglyceride-lowering activity[d]
82	CH_3-	45.1	147—148	Et	$C_{19}H_{20}N_2O_3S \cdot HCl$	1[e]	1[e]
83		28.7	126—128	Pr	$C_{20}H_{22}N_2O_3S$	1[e]	1[e]
84	CH_3 CH_3-	47.3	141—142	Et	$C_{21}H_{24}N_2O_3S \cdot HCl$	3	2
85	CH_3CH_2-	41.2	89—97	E-PE	$C_{21}H_{24}N_2O_3S$	2	1
86	$(C_2H_5)_2N$-CH_2CH_2-	59.8	100—101	EA-H	$C_{25}H_{33}N_3O_3S$	1	1
87	N-CH_2CH_2-	39.6	149—152	Et	$C_{24}H_{24}N_2O_3S$	1[e]	1[e]
88	O N-CH_2CH_2-	41.6	209—213	C-M	$C_{28}H_{28}N_2O_5S$	1	1
89	CH_2CH_2-	36.8	75—77	EA-L	$C_{21}H_{21}NO_3S$	3	4
100	N CH_2CH_2-	54.5	165—170	M	$C_{20}H_{19}N_3O_3S$	5	2
101	N CH_2CH_2-	4.4	167—168	Et	$C_{20}H_{19}N_3O_3S$	5[e]	5[e]

a) Yield from the corresponding methyl 2-(2-alkoxy-5-methylbenzyl)-2-chloropropionate. Prepared by Method B.
b) The methods a, d or e in Table I, respectively.
c) The data of CHN (±0.4%).
d) Dose 0.03% (w/w).

Results and Discussion

The structures, physical constants and biological data of the thiazolidine-2,4-dione derivatives are shown in Tables I—VII.

Since compound 1 (AL-321) was first found to possess potent hypoglycemic and hypolipidemic activities,[1] various compounds having modified phenethyl moieties, as shown in Table I, have been synthesized. All the compounds, especially 12, 15 and 18, had pronounced hypoglycemic and hypolipidemic activities. Although slight potentiation of the biological activity was noted when the methyl groups on the side chain of 1 were removed (1 vs. 10), introduction of substituent(s) on the benzene ring of the phenethyl moiety did not alter the activities (1 vs. 2—9, 10 vs. 11—20).

Variation of the distance between the two benzene rings as listed in Table II indicated that the two-carbon unit was the most effective for eliciting the activity (1, 10, 24, 25>21, 23, 26; 16>31; 18>33).

Among the compounds listed in Tables I and II, compounds 10, 12, 15, 18 and 25 showed more potent activities than 1, but these compounds caused considerable increases in relative liver weight and liver lipid at high dose levels or on chronic administration. As this undesirable effect may have been a consequence of the existence of two benzene rings in the molecule, we replaced one of them with other moieties.

First, the phenethyl group of 10 was replaced by various alkyl groups. Such compounds, listed in Table III, exhibited good activities with reduced side effects. In particular, 40 (ADD-3878) showed a pronounced hypoglycemic effect and extremely low toxicity, though

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its triglyceride lowering effect was not prominent. Compound 49 (ADD-3878) might therefore have potential utility as an antidiabetic drug. Compound 52 was as effective as but more toxic than 49 (ADD-3878). Compound 47 also showed good activities with low toxicity.

A series of compounds bearing less hypophilic groups (i.e., pyridylalkyl, aminoalkyl, etc.) instead of aralkyl or alkyl groups was next investigated. Although compounds 56, 57, 58, 59 and 63 in Table IV showed potent activities, they, especially 57 and 58, caused considerable increases in body weight and brown fat weight. Compound 70, 72 and 73 also exhibited potent activities, but had some side effects.

Besides these compounds, those listed in Tables V and VI were also prepared, but they exhibited no valuable activities. The fact that compounds 85 and 88 were completely or nearly inactive suggests that the partial structure is the essential structural feature for both glucose- and triglyceride-lowering activities.

Table VII lists compounds having a pyridine ring instead of the benzene ring in the 4-oxybenzyl group. These compounds, except 99 and 101, had weaker activities than the corresponding 4-oxybenzyl derivatives.

Conclusion

In a search for antidiabetic agents, we prepared a series of compounds related to thiazolidine-2,4-dione derivatives and evaluated their potential hypoglycemic and hypolipidemic activities in genetically obese and diabetic mice, yellow KK. Compounds 47, 49 (ADD-3878) and 59 exhibited the most favorable profiles in terms of activity and toxicity. These compounds may be valuable for the treatment of maturity-onset diabetes and/or hyperlipidemia which involves obesity.

Experimental

Melting points were determined on Yanagimoto micro melting point apparatus and are uncorrected. IR spectra were taken on a Hitachi IR-215 spectrophotometer. NMR spectra were recorded on a Varian T-60 NMR spectrometer in $CDCl_3$ unless otherwise noted. Chemical shifts are given in ppm with tetramethylsilane as the internal standard and coupling constants (J) are given in Hz. The following abbreviations are used, s=singlet, br s=broad singlet, d=doublet, t=triplet, q=quartet, m=multiplet.

Nitro Compounds VIII and XII

Typical examples are given to illustrate the general procedure.

4-[2-(3-Methoxyphenyl)-2-methylpropoxy]nitrobenzene —A stirred mixture of 2-(3-methoxyphenyl)-2-methyl-1-propanol (10.9 g), *p*-chloronitrobenzene (8.8 g) and dimethylsulfoxide (DMSO) (100 ml) was treated portionwise with 50% NaH in oil (3.2 g) at 45°C. The mixture was stirred at 70°C for 80 min, poured into H_2O, acidified with 3 *n* HCl and extracted with Et_2O. The usual work-up gave crystals (12.7 g, 79.7%). Recrystallization from MeOH gave colorless prisms, mp 80—80°C. IR ν_{max}^{Nujol} cm^{-1}: 1510, 1340. NMR δ: 1.43 (6H, s), 3.78 (3H, s), 4.00 (2H, s), 6.6—7.6 (8H, m), 8.03 (2H, d, J=9), 8.17 (2H, d, J=9). *Anal.* Calcd for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65. Found: C, 67.70; H, 6.37; N, 4.66.

4-[2-(2-Pyridyl)ethoxy]nitrobenzene —A stirred and ice-cooled solution of 2-(2-pyridyl)ethanol (25.0 g) and *p*-fluoronitrobenzene (30.6 g) in dimethylformamide (DMF) (200 ml) was treated portionwise with 50% NaH in oil (19 g). The mixture was stirred with ice-cooling for 1 h and diluted with H_2O. The crystalline solid was filtered off and recrystallized from MeOH to give light yellow prisms (29.0 g, 58.5%), mp 76—77°C. IR ν_{max}^{Nujol} cm^{-1}: 1500, 1335. NMR δ: 3.27 (2H, t, J=7), 4.50 (2H, t, J=7), 6.90 (2H, d, J=9), 7.6—7.9 (3H, m), 8.13 (2H, d, J=9), 8.46 (1H, m). *Anal.* Calcd for $C_{13}H_{12}N_2O_3$: C, 63.92; H, 4.95; N, 11.47. Found: C, 64.16; H, 4.92; N, 11.38.

The 4-alkoxynitrobenzenes (VIII) listed in Table VIII were similarly prepared. The unlisted compounds were reported in preceding papers.[8]

2-(2-Morpholinoethoxy)-5-nitropyridine —A stirred and ice-cooled solution of 2-chloro-5-nitropyridine (15.9 g) and 2-morpholinoethanol (13.1 g) in anhydrous tetrahydrofuran (THF) (200 ml) was treated portionwise with 60% NaH in oil (4.4 g). The mixture was stirred with ice-cooling for 1 h, diluted with H_2O (1 l) and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give

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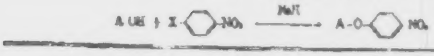
Table VIII. Nitro Compounds (VIII)



A	X	Yield (%)	mp (°C)	Recryst. solvent[a]	Formula[b]
4-CH_3O-$C_6H_4C(CH_3)_2CH_2$-	Cl	80.6	78–79	M	$C_{20}H_{25}NO_3$
4-$C_{13}H_{27}$-$C_6H_4C(CH_3)_2CH_2$-	Cl	32.4	66–67	M	$C_{19}H_{23}NO_3$
4-$C_8H_{17}O$-$C_6H_4C(CH_3)_2CH_2$-	Cl	70.3	59–60	M	$C_{19}H_{23}NO_4$
4-$C_6H_5CH_2O$-$C_6H_4C(CH_3)_2CH_2$-	Cl	83.1	120–121	M	$C_{23}H_{23}NO_4$
3,4-$(CH_3O)_2$-$C_6H_3C(CH_3)_2CH_2$-	Cl	60.4	63–64	M	$C_{20}H_{25}NO_4$
4-CH_3-$C_6H_3CH_2CH_2$-	Cl	35.3	Oil	—	$C_{20}H_{25}NO_3$
2-CH_3O-$C_6H_3CH_2CH_2$-	Cl	58.9	91–92	M	$C_{20}H_{25}NO_4$
4-CH_3O-$C_6H_3CH_2CH_2$-	Cl	72.3	56–57	M	$C_{20}H_{25}NO_4$
4-C_6H_5-$C_6H_4CH_2CH_2$-	Cl	62.0	Oil	—	$C_{26}H_{27}NO_3$
4-C_6H_5O-$C_6H_4CH_2CH_2$-	F	77.9	85–87	M	$C_{26}H_{27}NO_4$
4-Cl-$C_6H_3CH_2CH_2$-	F	68.0	67–68	M	$C_{19}H_{21}ClNO_3$
2-CH_3O-4-CH_3-$C_6H_3CH_2CH_2$-	F	79.2	80–81	M	$C_{21}H_{27}NO_4$
3,4-$(CH_3O)_2$-$C_6H_3CH_2CH_2$-	Cl	66.9	93–94	M	$C_{21}H_{27}NO_5$
3,4,5-$(CH_3O)_3$-$C_6H_2CH_2CH_2$-	F	60.4	108–110	M	$C_{22}H_{29}NO_6$
3,4-(-OCH_2O-)-$C_6H_3CH_2CH_2$-	F	68.9	79–80	M	$C_{21}H_{25}NO_5$
$(C_6H_5)_2CHCH_2$-	F	89.0	132–133	Et	$C_{26}H_{27}NO_3$
$(C_6H_5)_2C(CH_3)CH_2$-	Cl	76.1	115–118	M	$C_{27}H_{29}NO_3$
	Cl	51.3	99–100	Et	$C_{20}H_{23}NO_3$
$CH_3CH_2C(CH_3)_2CH_2$-	Cl	86.0	Oil	—	$C_{15}H_{23}NO_3$
$CH_3(CH_2)_3C(CH_3)_2CH_2$-	Cl	73.9	Oil	—	$C_{16}H_{25}NO_3$
$CH_3(CH_2)_5C(CH_3)_2CH_2$-	Cl	57.9	Oil	—	$C_{18}H_{29}NO_3$
Geranyl-	Cl	36.5	Oil	—	$C_{20}H_{31}NO_3$
Phytyl-	F	79.5	Oil	—	$C_{36}H_{63}NO_4$
CH_2=CH-$CH_2C(CH_3)_2CH_2$-	Cl	74.2	Oil	—	$C_{15}H_{21}NO_3$
Geranyl-$C(CH_3)_2CH_2$-	Cl	61.2	Oil	—	$C_{20}H_{29}NO_3$
	F	78.1	Oil	—	$C_{20}H_{27}NO_3$
	F	75.0	Oil	—	$C_{20}H_{27}NO_4$
	F	75.5	77–78	M	$C_{20}H_{25}NO_4$
	Cl	62.0	67–68	M	$C_{21}H_{27}NO_4$
	Cl	86.5	59–60	Et–W	$C_{20}H_{31}NO_3$
	F	80.0	Oil	—	$C_{20}H_{27}NO_4$
	Cl	72.1	Oil	—	$C_{20}H_{29}NO_3$
	Cl	63.0	47–48	M	$C_{19}H_{27}NO_3$
Isobornyl-	Cl	78.5	100–110	M	$C_{20}H_{29}NO_3$
Dunnyl-	Cl	78.8	107–108	M	$C_{20}H_{29}NO_3$
l-Menthyl-	Cl	80.3	64–65	M	$C_{20}H_{29}NO_3$
	Cl	62.9	135–136	M	$C_{20}H_{18}N_2O_3$
	F	79.9	61–62	M	$C_{21}H_{20}N_2O_3$
	F	75.0	104–105	M	$C_{20}H_{18}N_2O_3$
	F	78.7	86–87	M	$C_{21}H_{20}N_2O_3$
	F	67.2	63–64	M	$C_{17}H_{17}NO_3S$

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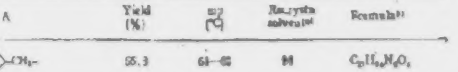
A	X	Yield (%)	mp (°C)	Recryst. solvent[a]	Formula[b]
	F	57.2	52—54	M	$C_{20}H_{21}NO_4$
	F	85.6	93—95	M	$C_{20}H_{21}NO_3S$
	F	82.2	Oil	—	$C_{20}H_{23}N_3O_4$
$(CH_3)_2CHNH\text{-}CH_2CH_2$-	F	72.1	215—218	M–E	$C_{20}H_{25}N_3O_4 \cdot HCl$
$(CH_3)_2NH\text{-}CH_2CH_2$-	F	70.5	241—244	M–P	$C_{20}H_{25}N_3O_4 \cdot HCl$
$(C_2H_5)_2N\text{-}CH_2CH_2$-	Cl	61.6	162—163	M–E	$C_{20}H_{25}N_3O_4 \cdot HCl$
$(C_2H_5)_2N\text{-}CH_2CH_2$-	Cl	71.0	Oil	—	$C_{20}H_{25}N_3O_4$
$(iso\text{-}C_3H_7)_2N\text{-}CH_2CH_2$-	Cl	67.2	Oil	—	$C_{22}H_{29}N_3O_4$
	F	82.4	82—83	EA–H	$C_{20}H_{23}N_3O_4$
	Cl	89.1	201—202	EA–W	$C_{20}H_{23}N_3O_4 \cdot HCl \cdot 2H_2O$
	Cl	93.3	195—196	EA–E	$C_{20}H_{23}N_3O_4 \cdot HCl$
	Cl	88.5	210—211	M–E	$C_{20}H_{23}N_3O_4 \cdot HCl$

a) E=Et$_2$O, EA=AcOEt, P=PrOH, M=MeOH, W=H$_2$O.
b) All compounds were analyzed for C, H and N, analytical results obtained for these elements were within ±0.4% of calculated values. Oily compounds were purified by column chromatography and used for the subsequent reactions.

Table IX. Nitro Compounds (XII)



A	Yield (%)	mp (°C)	Recryst. solvent[a]	Formula[b]
	55.3	64—65	M	$C_{20}H_{24}N_2O_3$
	52.7	Oil	—	$C_{18}H_{20}N_2O_3$
	42.2	38—39	E–H	$C_{19}H_{22}N_2O_3$
	89.9	58—59	M	$C_{20}H_{24}N_2O_3$
$(C_2H_5)_2N\text{-}CH_2CH_2$-	52.1	Oil	—	$C_{18}H_{25}N_3O_3$
	51.0	71—72	W	$C_{19}H_{23}N_3O_3$
	78.0	72—73	Et	$C_{20}H_{24}N_2O_3$
	75.5	56—57	E–H	$C_{19}H_{22}N_2O_3$
	80.2	116—117	M	$C_{19}H_{23}N_3O_3$

a, b) See the corresponding footnotes in Table VIII.

crystals (20.0 g, 79.1%). Recrystallization from EtOH gave light yellow prisms, mp 77—78°C. IR ν_{max}^{KBr} cm^{-1}: 1575, 1345. NMR δ: 2.60 (4H, t, J=6), 3.70 (4H, t, J=6), 4.64 (2H, t, J=6), 6.92 (1H, d, J=9), 8.41 (1H, q, J=9 and 3), 9.12 (1H, d, J=3). *Anal.* Calcd for $C_{14}H_{19}N_3O_4$: C, 58.17; H, 6.62; N, 16.69. Found: C, 58.21; H, 6.91; N, 16.47.

The 2-alkoxy-5-nitropyridines (XII) listed in Table IX were similarly prepared.

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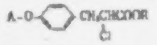
Table X. 3-Aryl-2-chloropropionic Acids (I)



A	R	Yield[a] (%)	Formula[b]
3-CH_3O-4-$C_6H_5CH_2O$-CH_2-	Me	54.0	$C_{17}H_{17}ClO_4$
4-CH_3O-3-$C_6H_5CH_2O$-CH_2-	Me	49.0	$C_{17}H_{17}ClO_4$
4-(2,4-F_2-C_6H_3)-CH_2-	Me	60.7	$C_{11}H_9F_2ClO_2$
4-C_6F_5O-C_6F_4-CH_2-	Me	49.7	$C_{16}H_7F_6ClO_3$
4-HO-3-CH_3O-C_6H_3-CH_2-	Et	46.0	$C_{12}H_{15}ClO_4$
3,4-(CH_2O_2)-C_6H_3-CH_2-	Me	50.0	$C_{11}H_{11}ClO_4$
4-CH_3-C_6H_4-CH_2-	Et	40.7	$C_{12}H_{15}ClO_2$
2-CH_3O-$C_6H_4CH_2$-	Me	41.6	$C_{11}H_{13}ClO_3$
4-CH_3O-$C_6H_4CH_2$-	Me	47.8	$C_{11}H_{13}ClO_3$
4-C_6H_5-$C_6H_4CH_2$-	Me	64.0	$C_{16}H_{15}ClO_2$
4-C_6H_5O-$C_6H_4CH_2$-	Me	51.7	$C_{16}H_{15}ClO_3$
4-Cl-$C_6H_4CH_2$-	Me	26.1	$C_{10}H_{10}Cl_2O_2$
2-CH_3O-, 4-CH_3-$C_6H_3CH_2$-	Me	60.9	$C_{12}H_{15}ClO_3$
2,4-(CH_3O)$_2$-$C_6H_3CH_2$-	Me	46.7	$C_{12}H_{15}ClO_4$
3,4,5-(CH_3O)$_3$-C_6H_2-CH_2-	Me	64.0	$C_{13}H_{17}ClO_5$
3,4-(-OCH_2O-)-$C_6H_3CH_2$-	Me	68.7	$C_{11}H_{11}ClO_4$
(C_6H_5)$_2$CH-CH_2-	Et	67.5	$C_{18}H_{19}ClO_2$
(C_6H_5)$_2$C(CH_3)-CH_2-	Et	78.0	$C_{19}H_{21}ClO_2$
	Et	78.5	$C_{20}H_{23}ClO_2$
C_6H_5-CH_2-	Et	63.3	$C_{13}H_{17}ClO_2$
$CH_3CH_2C(CH_3)_2CH_2$-	Me	60.9	$C_{13}H_{17}ClO_2$
$CH_3(CH_2)_2C(CH_3)_2CH_2$-	Et	64.1	$C_{15}H_{21}ClO_2$
$CH_3(CH_2)_3C(CH_3)_2CH_2$-	Et	58.8	$C_{16}H_{23}ClO_2$
Geranyl-	Et	60.3	$C_{18}H_{29}ClO_2$
Phytyl-	Et	56.0	$C_{24}H_{41}ClO_2$
CH_2=CH-$CH_2C(CH_3)_2CH_2$-	Et	58.8	$C_{15}H_{19}ClO_2$
Geranyl-$C(CH_3)_2CH_2$-	Et	54.0	$C_{20}H_{33}ClO_2$
	Me	77.1	$C_{10}H_{11}ClO_2$
	Me	75.6	$C_{10}H_{11}ClO_2$
	Me	78.5	$C_{11}H_{13}ClO_2$
	Me	73.2	$C_{12}H_{15}ClO_2$
	Et	76.7	$C_{13}H_{17}ClO_2$
	Me	78.1	$C_{13}H_{15}ClO_2$
Isobornyl-	Me	75.0	$C_{14}H_{21}ClO_2$
Bornyl-	Me	74.3	$C_{14}H_{21}ClO_2$
l-Menthyl-	Me	78.8	$C_{14}H_{25}ClO_2$
	Me	64.3	$C_{11}H_{10}ClNO_2$
	Me	61.2	$C_{12}H_{12}ClNO_2$
	Me	80.1	$C_{12}H_{11}Cl_2NO_2$
	Me	53.3	$C_{12}H_{12}ClNO_2$
	Me	63.8	$C_{13}H_{14}ClNO_2$

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A	R	Yield[a] (%)	Formula[b]
	Me	72.7	$C_{20}H_{22}ClO_3S$
	Me	96.4	$C_{20}H_{22}ClO_3$
	Me	67.9	$C_{20}H_{23}ClNO_3S$
	Me	65.1	$C_{20}H_{20}ClNO_4$
$(CH_3)_2CHNH\text{-}CH_2CH_2$-	Me	37.8	$C_{17}H_{24}ClNO_3$
$(CH_3)_2CHN\text{-}CH_2CH_2$-	Me	48.3	$C_{18}H_{26}ClNO_3$
$(C_2H_5)_2N\text{-}CH_2CH_2$-	Me	53.6	$C_{18}H_{26}ClNO_3$
$(C_2H_5)_2N\text{-}CH_2CH_2$-	Me	53.5	$C_{18}H_{26}ClNO_3$
$(iso\text{-}C_3H_7)_2N\text{-}CH_2CH_2$-	Me	59.8	$C_{20}H_{30}ClNO_3$
	Me	45.1	$C_{19}H_{24}ClNO_3$
	Me	31.6	$C_{20}H_{25}ClN_2O_3$
	Me	48.1	$C_{20}H_{24}ClNO_3$
	Me	52.7	$C_{21}H_{26}ClNO_3$

a) Overall yield from the corresponding nitro compound (VIII).
b) All compounds were oily products and were purified by column chromatography on silica gel.

3-Aryl-2-chloropropionic Acids (I)

Typical examples are given to illustrate the general procedure.

Methyl 2-Chloro-3-[4-(1-methylcyclohexylmethoxy)phenyl]propionate — A mixture of 4-(1-methylcyclohexylmethoxy)nitrobenzene (50.2 g), 10% Pd-C (2.0 g) and MeOH (400 ml) was hydrogenated at room temperature and atmospheric pressure. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. The residual oil was dissolved in acetone (500 ml). To this stirred and ice-cooled solution, conc. HCl (66 ml) and a solution of $NaNO_2$ (18.9 g) in H_2O (40 ml) were added dropwise below 5°C. The whole was stirred at 5°C for 30 min, then methyl acrylate (124 g) was added thereto and the temperature was raised to 25°C. Cu_2O (0.3 g) was added to the mixture in small portions with vigorous stirring. After N_2 gas evolution had ceased, the reaction mixture was concentrated *in vacuo*, diluted with H_2O and extracted with Et_2O. The usual work-up gave a crude oil, which was purified by column chromatography on silica gel (700 g) using Et_2O–hexane (1: 19, v/v) as an eluent to give a pure oil (51.8 g, 77.8%). IR ν_{max}^{film} cm^{-1}: 1745. NMR (C_6D_6) δ: 1.0 (3H, s), 1.30 (12H, br s), 2.80 (1H, q, J=14 and 7), 3.19 (1H, q, J=14 and 7), 3.34 (2H, s), 3.45 (3H, s), 4.30 (1H, t, J=7), 6.75 (2H, d, J=8), 6.98 (2H, d, J=8). The ester was converted to the corresponding acid by the usual alkaline hydrolysis in quantitative yield, mp 104—106°C (from hexane). IR ν_{max}^{Nujol} cm^{-1}: 1710. NMR δ: 1.0 (3H, s), 1.43 (12H, br s), 2.86 (1H, q, J=14 and 7), 3.31 (1H, q, J=14 and 7), 3.40 (2H, s), 4.19 (1H, t, J=7), 6.81 (2H, d, J=8), 7.19 (2H, d, J=8), 10.56 (1H, br s). *Anal.* Calcd for $C_{20}H_{29}ClO_3$: C, 68.09; H, 8.48. Found: C, 68.60; H, 7.30.

The 3-(4-alkoxyphenyl) 2-chloropropionates listed in Table X were similarly prepared. The related compounds were reported in preceding papers.[3]

Methyl 2-Chloro-3-[5-[2-(3-pyridyloxy)-3-pyridyl]-2-pyridyl]propionate — A mixture of 5-nitro-2-[2-(3-pyridyloxy)ethoxy]pyridine (15.0 g), 10% Pd-C (2.0 g) and MeOH (150 ml) was hydrogenated at room temperature and atmospheric pressure. After removal of the catalyst by filtration, acetone (100 ml) was added to the filtrate. To the stirred and ice-cooled solution, conc. HCl (26 ml) and a solution of $NaNO_2$ (4.6 g) in H_2O (10 ml) were added dropwise below 5°C. The mixture was stirred at 5°C for 30 min and methyl acrylate (35 g) was added thereto. The temperature was raised to 35°C and Cu_2O (1.0 g) was added to the mixture in small portions with vigorous stirring. After N_2 gas evolution had ceased, the reaction mixture was concentrated *in vacuo*, diluted with H_2O, neutralized with conc. NH_4OH and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residual oil was chromatographed on silica gel (150 g) using Et_2O–hexane–Et_3N (36: 35: 1, v/v) as an eluent to give a pure oil (1.5 g, 33.3%). IR ν_{max}^{film} cm^{-1}: 1736. NMR δ: 3.09 (2H, t, J=7), 3.0—3.5 (2H, m), 3.75 (3H, s), 4.63 (1H, t, J=7), 4.57 (2H, t, J=7), 6.75 (1H, d, J=8), 7.2—7.8 (5H, m), 8.02 (1H, d, J=2), 8.3—8.7 (2H, m).

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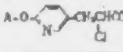
Table XI. Methyl 3-(2-Alkoxy-4-pyridyl)-2-chloropropionates (I)



A	Yield[a] (%)	Formula[b]
	60.2	$C_{20}H_{20}ClNO_3$
	41.2	$C_{20}H_{20}ClNO_3$
	38.7	$C_{21}H_{22}ClNO_3$
	63.9	$C_{21}H_{22}ClNO_3$
	19.6	$C_{20}H_{19}ClN_2O_3$
	53.5	$C_{20}H_{21}ClN_2O_3$
	58.5	$C_{20}H_{21}ClN_2O_3$
	74.6	$C_{20}H_{19}ClNO_3$
	27.5	$C_{19}H_{19}ClN_2O_3$

a, b) See the corresponding footnotes in Table X.

The 3-(2-alkoxy-4-pyridyl)-2-chloropropionates listed in Table XI were similarly prepared.

Thiazolidine-2,4-diones (II)

Typical examples are given to illustrate the general procedure.

Method A——5-[4-[(1-Methylcyclohexyl)methoxy]benzyl]thiazolidine-2,4-dione (49, ADD-3878): A mixture of 2-(p-iso-5-[4-[(1-methylcyclohexyl)methoxy]benzyl]thiazolidin-4-one (8.0 g), 3 N HCl (10 ml) and 2-methoxyethanol (60 ml) was refluxed for 6 h, cooled and diluted with H_2O to give crystals of 49. Recrystallization from 85% EtOH gave colorless plates (5.3 g, 51.3%), mp 130—131°C. IR ν_{max}^{Nujol} cm^{-1}: 3100, 3050, 1780, 1645. NMR δ: 1.03 (3H, s), 1.47 (10H, br s), 3.08 (1H, q, J=14 and 9), 3.48 (1H, q, J=14 and 4), 3.47 (2H, s), 4.55 (1H, q, J=9 and 4), 6.52 (2H, d, J=9), 7.33 (2H, d, J=9), 8.12 (1H, br s). *Anal.* Calcd for $C_{24}H_{33}NO_3S$: C, 66.94; H, 6.98; N, 4.20. Found: C, 64.78; H, 6.88; N, 4.18.

The starting material used for this method was prepared as follows:

2-Imino-5-[4-[(1-methylcyclohexyl)methoxy]benzyl]thiazolidin-4-one: A mixture of methyl 2-chloro-3-[4-[(1-methylcyclohexyl)methoxy]phenyl]propionate (13.2 g), thiourea (5.0 g), NaOAc (3.3 g) and 2-methoxyethanol (80 ml) was stirred at 100°C for 10 h and concentrated *in vacuo*. H_2O (50 ml)–hexane (50 ml) was added to the residue and the insoluble solid was filtered off (10.5 g, 80.4%). Recrystallization from EtOH gave colorless prisms, mp 263—264°C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 3210, 1685. NMR (d_6-DMSO) δ: 0.96 (3H, s), 1.40 (10H, br s), 2.70 (1H, q, J=14 and 9), 3.35 (1H, q, J=14 and 4), 3.62 (2H, s), 4.40 (1H, q, J=9 and 4), 6.82 (2H, d, J=9), 7.12 (2H, d, J=9), 8.65 (1H, br s), 8.85 (1H, br s). *Anal.* Calcd for $C_{18}H_{24}N_2O_2S$: C, 65.89; H, 7.39; N, 8.62. Found: C, 64.92; H, 7.31; N, 8.27.

The 2-iminothiazolidin-4-ones (II) listed in Table XII were similarly prepared.

Method B——5-[4-[2-(3-Methoxy-4-methylphenyl)ethoxy]benzyl]thiazolidine-2,4-dione (17): A mixture of methyl 2-chloro-3-[4-[2-(3-methoxy-4-methylphenyl)ethoxy]phenyl]propionate (12.0 g), thiourea (5.5 g) and sulfolane (150 ml) was stirred at 130°C for 10 h, then 2 N HCl (50 ml) was added thereto. The mixture was stirred at 100°C for 8 h, cooled, diluted with H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give 17 as crystals (10.5 g, 78.9%). Recrystallization from AcOEt–hexane gave colorless prisms, mp 92—93°C. IR ν_{max}^{Nujol} cm^{-1}: 3180, 1750, 1690. NMR δ: 2.14 (3H, s), 3.02 (1H, q, J=14 and 9), 3.05 (2H, t, J=7), 3.47 (1H, q, J=14 and 4), 3.80 (3H, s), 4.32 (2H, t, J=7), 4.45 (1H, q, J=9 and 4), 6.8—7.4 (7H, m), 9.45 (1H, br s). *Anal.* Calcd for $C_{20}H_{21}NO_4S$: C, 64.68; H, 5.70; N, 3.77. Found: C, 64.56; H, 5.59; N, 3.61.

Method C——5-[4-[(1-Methylcyclohexyl)methoxy]benzyl]thiazolidine-2,4-dione (49, ADD-3878): A mixture of methyl 3-[4-[(1-methylcyclohexyl)methoxy]phenyl]-2-thioxopropionate (3.0 g), 6 N HCl (20 ml) and EtOH (20 ml) was refluxed for 60 h, cooled, diluted with H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give 49 as crystals (1.38 g, 70.9%). Recrystallization from 85% EtOH gave colorless plates, mp 130—131°C. This sample was identical with an authentic sample of 49 prepared by method A.

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TABLE XII 2-Imonothiazolidin-4-ones (II)

A	Yield[a] (%)	mp (°C)	Recrystn. solvent[b]	Formula[c]
Geranyl-	54.9	189—190	A	$C_{20}H_{33}NO_2S$
Phytyl	62.9	173—174	A	$C_{30}H_{57}NO_2S$
	66.7	280—281[d]	Et	$C_{20}H_{29}NO_2S$
	78.0	253—254[d]	Et	$C_{20}H_{29}NO_2S$
	74.1	237—238[d]	Et	$C_{20}H_{29}NO_2S$
	72.0	233—234[d]	Et	$C_{20}H_{29}NO_2S$
	75.6	250—252[d]	Et	$C_{20}H_{29}NO_2S$
Isobornyl-	70.5	283—284[d]	Et	$C_{20}H_{33}NO_2S$
Bornyl-	80.6	280—282[d]	Et	$C_{20}H_{33}NO_2S$
l-Menthyl-	75.1	236—238[d]	Et	$C_{20}H_{33}NO_2S$
	50.0	191—192	EA–M	$C_{20}H_{31}NO_2S$

a) Yield from the corresponding 3-aryl-2-chloropropionic acid (I).
b) Rec.
c) A = acetone EA = AcOEt, Et = EtOH, M = MeOH.
d) All compounds were analyzed for C, H and N; analytical results obtained for these compounds were within 0.4% of calculated values.

The starting materials used for this method were prepared as follows.

Methyl 3-[4-[1-Methylcyclohexylmethoxy]phenyl]-3-thiocyanatopropionate: A mixture of methyl 3-chloro-3-[4-(1-methylcyclohexylmethoxy)phenyl]propionate (8.35 g), potassium thiocyanate (1.46 g) and DMSO (35 ml) was stirred at 100°C for 3 h, poured into H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give crystals (8.18 g, 91.8%). Recrystallization from benzene gave colorless needles, mp 54—55°C. IR ν_{max}^{KBr} cm^{-1}: 2160, 1730. NMR δ: 1.00 (3H, s), 1.13 (10H, br s), 3.13 (1H, q, J=14 and 7), 3.38 (1H, q, J=14 and 7), 3.82 (2H, s), 3.78 (3H, s), 3.94 (1H, t, J=7), 6.88 (2H, d, J=9), 7.12 (2H, d, J=9). *Anal.* Calcd for $C_{19}H_{25}NO_3S$: C, 65.60; H, 7.36; N, 4.03. Found: C, 65.74; H, 7.47; N, 4.16.

The following compounds were similarly prepared.

Ethyl 3-[4-(3-Methyl-2-phenylpropoxy)phenyl]-3-thiocyanatopropionate: Oil. Yield 90.8%. IR ν_{max}^{neat} cm^{-1}: 2160, 1735. NMR δ: 1.20 (3H, t, J=7), 1.63 (3H, s), 2.13 (1H, q, J=14 and 7), 3.22 (1H, q, J=14 and 7), 3.83 (1H, t, J=7), 3.90 (2H, s), 4.15 (2H, q, J=7), 6.82 (2H, d, J=9), 7.00 (2H, d, J=9), 7.2—7.6 (5H, m).

Ethyl 3-[4-(2,2-Dimethylpropoxy)phenyl]-3-thiocyanatopropionate: Oil. Yield 83.4%. IR ν_{max}^{neat} cm^{-1}: 2165, 1735. NMR δ: 1.03 (9H, s), 1.30 (3H, t, J=7), 3.10 (1H, q, J=14 and 7), 3.35 (1H, q, J=14 and 7), 3.56 (2H, s), 3.92 (1H, t, J=7), 4.25 (2H, q, J=7), 6.82 (2H, d, J=9), 7.13 (2H, d, J=9).

Ethyl 3-[4-(3,3-Dimethyl-2-phenylpropoxy)phenyl]-3-thiocyanatopropionate: Oil. Yield 80.0%. IR ν_{max}^{neat} cm^{-1}: 2160, 1735. NMR δ: 1.0 (6H, s), 1.33 (3H, t, J=7), 2.67 (2H, s), 3.10 (1H, q, J=14 and 7), 3.30 (1H, q, J=14 and 7), 3.47 (2H, s), 3.80 (1H, t, J=7), 4.17 (2H, q, J=7), 6.77 (2H, d, J=9), 7.08 (2H, d, J=9), 7.10 (5H, br s).

Ethyl 3-[4-(3-Phenylpropoxy)phenyl]-3-thiocyanatopropionate: Oil. Yield 88.1%. IR ν_{max}^{neat} cm^{-1}: 2165, 1736. NMR δ: 1.31 (3H, t, J=7), 1.9—2.4 (2H, m), 2.76 (2H, t, J=7), 3.14 (1H, q, J=14 and 7), 3.21 (1H, q, J=14 and 7), 3.85 (2H, t, J=7), 3.99 (1H, t, J=7), 4.14 (2H, q, J=7), 6.74 (2H, d, J=9), 7.06 (2H, d, J=9), 7.12 (5H, s).

Method D——5-[4-[1-Methylcyclohexylmethoxy]benzyl]thiazolidine-2,4-dione (49, ADD-3878): A mixture of 3-bromo-3-[4-(1-methylcyclohexylmethoxy)phenyl]propionitrile (2.5 g), thiourea (0.86 g) and sulfolane (20 ml) was stirred at 110°C for 2 h, then 2*N* HCl (20 ml) was added thereto. The mixture was refluxed for 8 h, cooled, diluted with H_2O and extracted with Et_2O. The usual work-up gave 49 (2.6 g, 98.0%), mp 130—131°C (from 85% EtOH). This sample was identical with an authentic sample of 49

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prepared by method A.

The starting compounds used for this method were prepared as follows.

3-Bromo-4-[4-(3-methylcyclohexylmethoxy)phenyl]propionitrile: A mixture of 4-(3-methylcyclohexylmethoxy)nitrobenzene (8.0 g), 10% Pd/C (2.5 g) and MeOH (80 ml) was hydrogenated at room temperature and atmospheric pressure. The catalyst was filtered off and the filtrate was concentrated. The residual oil was dissolved in acetone (40 ml). To this stirred and ice-cooled solution, 47% HBr (72.5 g) and a solution of $NaNO_2$ (3.23 g) in H_2O (4 ml) were added dropwise below 5°C. The mixture was stirred at 5°C for 30 min, then acrylonitrile (7.6 g) was added thereto and the temperature was raised to 35°. Cu_2O (0.5 g) was added to the mixture in small portions with vigorous stirring. After N_2 gas evolution had ceased, the reaction mixture was concentrated, diluted with H_2O and extracted with Et_2O. The usual work-up gave a crude oil, which was purified by column chromatography on silica gel (80 g) using Et_2O–benzene (1: 10, v/v) as an eluent to give a pure oil (3.9 g, 48.1%). IR ν_{max}^{film} cm^{-1}: 2250. NMR δ: 1.02 (3H, d, 1.43 (10H, br sh), 3.25 (2H, d, J=7), 3.69 (2H, s), 4.37 (1H, t, J=7), 6.78 (2H, d, J=9), 7.10 (2H, d, J=9).

The following compound was similarly prepared.

3-Bromo-3-(4-cyclohexylmethoxyphenyl)propionitrile: Oil. Yield 43.8%. IR ν_{max}^{film} cm^{-1}: 2250. NMR δ: 1.2–2.2 (10H, br s), 3.15 (2H, d, J=7), 4.30 (1H, m), 4.32 (2H, t, J=7), 6.84 (2H, d, J=9), 7.14 (2H, d, J=9).

Method E——5-(4-Geranyloxybenzyl)thiazolidine-2,4-dione (41) and 3-Geranyl-5-(4-hydroxybenzyl)thiazolidine-2,4-dione (X, A=geranyl): A mixture of 57 (3.77 g, 50% NaH in oil (0.48 g) and DMSO (10 ml) was stirred at room temperature for 15 min and a solution of geranyl bromide (2.68 g) in DMSO (5 ml) was added thereto. The mixture was stirred at room temperature for 20 min, poured into H_2O, acidified with 2 N HCl and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residual oil was chromatographed on silica gel (80 g) with cyclohexane–AcOEt (4: 1, v/v). The first part of the eluate gave X (A=geranyl) (0.46 g, 35.0%), mp 85—86°C (from cyclohexane). IR ν_{max}^{Nujol} cm^{-1}: 3400—3500, 1760, 1660. NMR δ: 1.63 (3H, s), 1.68 (3H, s), 1.73 (3H, s), 2.0 (4H, m), 3.09 (1H, q, J=14 and 9), 3.42 (1H, q, J=14 and 4), 4.19 (2H, d, J=7), 4.37 (1H, q, J=9 and 4), 5.03 (1H, m), 5.37 (1H, m), 6.72 (2H, d, J=9), 7.03 (2H, d, J=9). *Anal.* Calcd for $C_{19}H_{25}NO_4S$: C, 63.83; H, 7.05; N, 3.92. Found: C, 63.81; H, 7.01; N, 3.81. The following part of the eluate gave 41 (0.9 g, 50.9%), mp 55—56°C (from cyclohexane–hexane). IR ν_{max}^{Nujol} cm^{-1}: 3200, 1760, 1660. NMR δ: 1.60 (3H, s), 1.67 (3H, s), 1.70 (3H, s), 2.1 (4H, m), 3.00 (1H, q, J=14 and 9), 3.43 (1H, q, J=14 and 4), 4.18 (1H, q, J=9 and 4), 4.61 (2H, d, J=7), 5.06 (1H, m), 5.28 (1H, t, J=7), 6.80 (2H, d, J=9), 7.10 (2H, d, J=9), 8.50 (1H, br s). *Anal.* Calcd for $C_{19}H_{25}NO_4S$: C, 63.83; H, 7.05; N, 3.92. Found: C, 63.78; H, 6.81; N, 3.83.

The following compounds were similarly prepared.

5-(4-Phytyloxybenzyl)thiazolidine-2,4-dione (42): mp 51—53°C (from hexane). Yield 40.9%. IR ν_{max}^{Nujol} cm^{-1}: 3230, 1760, 1710. NMR δ: 0.8—0.9 (12H, br d), 1.1—2.3 (34H, m), 3.07 (1H, q, J=14 and 9), 3.50 (1H, q, J=14 and 4), 4.44 (1H, q, J=9 and 4), 4.47 (2H, d, J=7), 5.43 (1H, t, J=7), 6.80 (2H, q, J=9), 7.11 (2H, d, J=9), 8.50 (1H, br s). *Anal.* Calcd for $C_{34}H_{55}NO_3S$: C, 71.91; H, 9.61; N, 2.79. Found: C, 72.10; H, 9.56; N, 2.60.

5-(4-Hydroxybenzyl)-3-phytylthiazolidine-2,4-dione (X, A=phytyl): Oil. Yield 21.9%. IR ν_{max}^{film} cm^{-1}: 3300—3200, 1740, 1670. NMR δ: 0.85—0.95 (12H, br s), 1.15—2.2 (34H, m), 3.10 (1H, q, J=14 and 9), 3.47 (1H, q, J=14 and 4), 4.50 (1H, q, J=9 and 4), 4.45 (2H, d, J=7), 5.46 (1H, t, J=7), 6.81 (2H, d, J=9), 7.15 (2H, d, J=9).

Method F——5-[4-(3-Pyrrolidinylmethoxy)benzyl]thiazolidine-2,4-dione Hydrochloride (84·HCl): A mixture of methyl 3-[4-(1-benzyl-3-pyrrolidinylmethoxy)phenyl]-2-chloropropionate (5.4 g), thiourea (1.8 g) and BuOH (40 ml) was stirred at 110°C for 13 h and concentrated in vacuo. The residue was extracted with $CHCl_3$, and the extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was dissolved in AcOH (40 ml) and conc. HCl (40 ml). The mixture was refluxed for 33 h, cooled, diluted with H_2O and extracted with AcOEt. The aqueous layer was concentrated in vacuo and EtOH (30 ml)–MeOH (5 ml) was added to the residue. The insoluble solid was filtered off and the filtrate was concentrated to leave a crystalline residue. Recrystallization from EtOH gave colorless prisms (1.9 g, 32.3%), mp 163—164°C. IR ν_{max}^{Nujol} cm^{-1}: 3350, 2700—2600, 1740, 1690. NMR (d$_6$-DMSO) δ: 1.7—2.2 (4H, m), 3.3—4.0 (9H, m), 4.12 (2H, d, J=6), 6.93 (1H, q, J=9 and 4), 6.99 (2H, d, J=9), 7.18 (2H, d, J=9), 10.2 (2H, br). *Anal.* Calcd for $C_{15}H_{18}N_2O_3S$·HCl: C, 53.96; H, 5.69; N, 8.37. Found: C, 53.66; H, 5.86; N, 7.72.

5-(4-Aminobenzyl)thiazolidine-2,4-dione (74): A mixture of 5-(4-nitrobenzyl)thiazolidine-2,4-dione (10.0 g), 10% Pd/C (10.0 g) and MeOH (250 ml)–AcOEt (150 ml) was hydrogenated at room temperature and atmospheric pressure. After removal of the catalyst by filtration, the filtrate was concentrated in vacuo to give crystals of 74 (7.8 g, 88.6%). Recrystallization from MeOH gave light yellow prisms, mp 183—185°C. IR ν_{max}^{Nujol} cm^{-1}: 3300, 3200, 3060 (br), 1755, 1690. NMR (d$_6$-DMSO) δ: 2.96 (1H, q, J=14 and 9), 3.25 (1H, q, J=14 and 4), 4.73 (1H, q, J=9 and 4), 6.48 (2H, d, J=9), 6.88 (2H, d, J=9), 7.5—9.0 (3H, br). *Anal.* Calcd for $C_{10}H_{10}N_2O_2S$: C, 54.05; H, 4.54; N, 12.61. Found: C, 54.08; H, 4.48; N, 12.75.

The starting material used for this method was prepared as follows.

Ethyl 3-Chloro-3-(4-nitrophenyl)propionate: Conc. HCl (25 ml) and a solution of $NaNO_2$ (1.8 g) in H_2O (15 ml) were added dropwise to a stirred and ice-cooled solution of *p*-nitroaniline (13.8 g) in acetone (150 ml) below 5°C. The whole was stirred at 5°C for 30 min, then ethyl acrylate (30 g) was added thereto and the

temperature was raised to 10°C. Et_2O (0.1 g) was added to the mixture in small portions with vigorous stirring. After N_2 gas evolution had ceased, the reaction mixture was concentrated in vacuo, diluted with H_2O and extracted with Et_2O. The usual work up gave an oily residue, which was purified by column chromatography on silica gel (140 g) using Et_2O–benzene (1: 10, v/v) as an eluent to give the title compound as an oil (16.5 g, 64.0%). IR ν_{max}^{film} cm^{-1}: 1735, 1510, 1345. NMR δ: 1.23 (3H, t, J=7), 3.28 (1H, q, J=14 and 7), 3.95 (3H, q, J=14 and 7), 4.15 (2H, q, J=7), 4.60 (1H, q, J=7), 7.36 (2H, d, J=9), 8.07 (2H, d, J=9).

5-[4-(Nitrobenzyl)thiazolidine-2,4-dione: A mixture of ethyl 2-chloro-3-[4-nitrophenyl]propionate (13.0 g), thiourea (7.6 g) and methanol (120 ml) was stirred at 130°C for 5 h and 2 N HCl (80 ml) was added thereto. The mixture was stirred at 100°C for 15 h, cooled and diluted with H_2O to give crystals. Recrystallization from MeOH gave colorless rods (9.0 g, 71.4%), mp 185—187°C. IR ν_{max}^{Nujol} cm^{-1}: 3250, 1750, 1695, 1345. NMR (d_6-DMSO) δ: 3.23 (1H, q, J=14 and 9), 3.87 (1H, q, J=14 and 4), 4.85 (1H, q, J=9 and 4), 7.45 (2H, d, J=9), 8.05 (2H, d, J=9), 11.9 (1H, br s). *Anal.* Calcd for $C_{10}H_8N_2O_5S$: C, 47.62; H, 3.20; N, 11.11. Found: C, 47.69; H, 3.31; N, 11.30.

5-[4-(p-Toluenesulfonylamino)benzyl]thiazolidine-2,4-dione (76): Reaction of 74 (4.0 g) and *p*-toluenesulfonyl chloride (3.5 g) gave the title compound (5.6 g, 96.6%), mp 224—225°C (from MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3220, 1740, 1690. NMR (d_6-DMSO) δ: 2.33 (3H, s), 3.07 (1H, q, J=14 and 9), 3.28 (1H, q, J=14 and 4), 4.79 (1H, q, J=9 and 4), 7.07 (4H, s), 7.32 (2H, d, J=9), 7.62 (2H, d, J=9), 10.13 (1H, s), 11.9 (1H, br s). *Anal.* Calcd for $C_{17}H_{16}N_2O_5S_2$: C, 54.28; H, 4.29; N, 7.44. Found: C, 54.18; H, 4.38; N, 7.32.

5-(4-Propionylaminobenzyl)thiazolidine-2,4-dione (76): Reaction of 74 (2.2 g) and propionyl chloride (1.0 ml) gave the title compound (1.56 g, 66.8%), mp 140—141°C (from AcOEt). IR ν_{max}^{Nujol} cm^{-1}: 3330, 1750, 1690, 1655. NMR (d_6-DMSO) δ: 1.10 (3H, t, J=7), 2.39 (2H, q, J=7), 3.00 (1H, q, J=14 and 9), 3.38 (1H, q, J=14 and 4), 4.83 (1H, q, J=9 and 4), 7.33 (2H, d, J=9), 7.85 (2H, d, J=9). *Anal.* Calcd for $C_{13}H_{14}N_2O_3S$: C, 56.11; H, 5.07; N, 10.07. Found: C, 55.79; H, 5.32; N, 9.83.

5-[4-Nicotinylaminobenzyl]thiazolidine-2,4-dione (77): Reaction of 74 (2.2 g) and nicotinoyl chloride [prepared from sodium nicotinate (1.74 g) and phosphorus oxytrichloride (0.97 g) according to the method of Russels *et al.*[6]] gave the title compound (1.0 g, 30.0%), mp 271—273°C (from DMF–H_2O). IR ν_{max}^{Nujol} cm^{-1}: 3360, 1740, 1690, 1670. NMR (d_6-DMSO) δ: 3.06 (1H, q, J=14 and 9), 3.38 (1H, q, J=14 and 4), 4.88 (1H, q, J=9 and 5), 7.37 (2H, d, J=9), 7.4—7.7 (1H, m), 7.76 (2H, d, J=9), 8.33 (1H, d, J=7), 8.8 (1H, m), 9.1 (1H, m), 10.08 (1H, br d), 11.9 (1H, br s). *Anal.* Calcd for $C_{16}H_{13}N_3O_3S$: C, 58.71; H, 4.00; N, 12.84. Found: C, 58.39; H, 4.01; N, 12.94.

5-[4-(3-Aminopropionylamino)benzyl]thiazolidine-2,4-dione Hydrobromide (78·HBr): A mixture of 5-[4-(3-benzyloxycarbonylaminopropionylamino)benzyl]thiazolidine-2,4-dione (1.9 g) and 25% HBr in AcOH (v/v, 20 ml) was stirred at room temperature for 30 min and diluted with Et_2O (100 ml). The crystalline precipitate was filtered off and recrystallized from MeOH to give 78·HBr (1.02 g, 41.6%), mp 242—243°C. IR ν_{max}^{Nujol} cm^{-1}: 2800, 2700—2300, 1750, 1690, 1640. NMR (d_6-DMSO) δ: 2.73 (2H, t, J=7), 2.9—3.5 (4H, m), 4.83 (1H, q, J=7 and 4), 7.18 (2H, d, J=9), 7.56 (2H, d, J=9), 7.9 (3H, br s), 10.17 (1H, s). *Anal.* Calcd for $C_{19}H_{19}N_3O_4S$·HBr: C, 41.72; H, 4.31; N, 11.53. Found: C, 41.36; H, 4.33; N, 11.10.

The starting material used for this method was prepared as follows.

5-[4-[3-Benzyloxycarbonylaminopropionylamino]benzyl]thiazolidine-2,4-dione: Et_3N (1.4 ml) and ethyl chloroformate (0.96 ml) were added dropwise to a stirred and ice-cooled solution of *N*-benzyloxycarbonyl-β-alanine (1.3 g). The mixture was stirred with ice-cooling for 15 min, and a solution of 74 (2.32 g) and Et_3N (1.4 ml) in CH_2Cl_2 (10 ml) was added dropwise thereto at −10°C. The reaction mixture was stirred at room temperature overnight, concentrated *in vacuo*, diluted with 2 N HCl (50 ml) and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$), and concentrated to leave an oil, which was treated with Et_2O to give the title compound (3.1 g, 73.8%) as a powder. Crystallization from EtOH–Et_2O gave colorless prisms, mp 189—191°C. IR ν_{max}^{Nujol} cm^{-1}: 3340, 1750, 1730, 1680. NMR (d_6-DMSO) δ: 2.4—2.7 (2H, m), 3.3—3.6 (4H, m), 4.89 (1H, q, J=8 and 5), 5.03 (2H, s), 7.1—7.6 (9H, m), 7.8 (1H, br d), 8.8 (1H, br s), 11.8 (1H, br s). *Anal.* Calcd for $C_{29}H_{29}N_3O_6S$: C, 59.89; H, 4.84; N, 9.82. Found: C, 59.88; H, 4.96; N, 9.66.

5-[4-[5-Aminobenzoylamino]benzyl]thiazolidine-2,4-dione (79): A mixture of 5-[4-[5-tert-butoxycarbonylaminobenzoylamino]benzyl]thiazolidine-2,4-dione (1.6 g) and 25% HBr in AcOH (v/v, 20 ml) was stirred at room temperature for 30 min then concentrated. The residue was charged on a column packed with Amberlite IRC-400 (AcO^-) (25 ml) and eluted with 20% MeOH (v/v). The solvent was evaporated off to give 79 as crystals (0.76 g, 47.9%), mp 216—218°C (from DMF–Et_2O). IR ν_{max}^{Nujol} cm^{-1}: 3400, 3300, 3250, 1670. NMR (d_6-DMSO) δ: 1.1—1.9 (6H, m), 2.5—3.4 (4H, m), 4.77 (1H, m), 7.1—7.7 (11H, m), 7.9 (2H, m), 9.8 (1H, br s), 11.8 (1H, br s). *Anal.* Calcd for $C_{17}H_{16}N_4O_4S$: C, 56.39; H, 4.30; N, 12.31. Found: C, 56.50; H, 4.45; N, 12.59.

The starting material used for this method was prepared as follows.

5-[4-[5-tert-Butoxycarbonylaminobenzoylamino]benzyl]thiazolidine-2,4-dione: Et_3N (1.4 ml) and ethyl chloroformate (0.96 ml) were added dropwise to a stirred and ice-cooled solution of 5-*tert*-butoxycarbonylaminobenzoic acid (2.15 g) in CH_2Cl_2 (10 ml). The mixture was stirred with ice-cooling for 10 min and a solution of 74 (2.2 g) and Et_3N (1.4 ml) in CH_2Cl_2 (10 ml) was added dropwise thereto at −10°C. The reaction mixture was stirred at −10°C for 30 min and at room temperature for 1 h, concentrated *in vacuo*, neutralized

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with 10% (w/w) citric acid aq. solution and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to leave the title compound as a crude oil (4.0 g, quant.). IR ν_{max}^{neat} cm^{-1}: 3050, 3130, 1760, 1710, 1600. NMR (d_6-DMSO) δ: 1.2—1.7 (6H, m), 1.36 (9H, s), 2.1—2.5 (2H, m), 2.8—3.5 (4H, m), 4.00 (1H, q, J=8 and 5), 6.58 (1H, br d), 7.1—7.6 (4H, m), 9.75 (1H, br s), 11.95 (1H, br s). The crude oil was used for the subsequent reaction without purification.

5-(4-Ethoxycarbonylmethyleneaminobenzoylamino-4-hexenyl)thiazolidine-2,4-dione (93): A solution of ethoxycarbonylmethylidenetriphenylphosphorane (2.65 g) in THF (5 ml) was added dropwise to a stirred and ice-cooled solution of 74 (1.1 g) in THF (10 ml). The mixture was stirred at 0°C for 1 h and at room temperature for 10 h, poured into H_2O and extracted with AcOEt. The usual work-up gave crystals of 93 (0.58 g, 38.7%). Recrystallization from EtOH gave colorless prisms, mp 161—162°C. IR ν_{max}^{Nujol} cm^{-1}: 3320, 3170, 1750, 1690. NMR δ: 1.28 (3H, t, J=7), 3.91 (1H, q, J=14 and 8), 3.43 (1H, q, J=14 and 4), 3.97 (2H, d, J=5), 4.18 (2H, q, J=7), 6.52 (1H, q, J=8 and 1), 6.87 (1H, q, J=5), 7.08 (2H, d, J=9), 7.36 (2H, d, J=9), 8.5 (1H, br s), 11.8 (1H, br s). *Anal.* Calcd for $C_{16}H_{17}N_3O_5S$: C, 51.21; H, 4.83; N, 11.96. Found: C, 51.11; H, 4.83; N, 11.77.

5-(4-Phenethylaminobenzoyl)thiazolidine-2,4-dione Hydrochloride (80·HCl): A mixture of 5-[4-[*N*-phenethyl-*N*-(*p*-toluenesulfonyl)amino]benzoyl]thiazolidine-2,4-dione (3.5 g), conc. H_2SO_4 (15 ml) and AcOH (15 ml) was stirred at 100°C for 1 h, cooled, neutralized with sat. aq. $NaHCO_3$ and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The oily residue was treated with a solution of HCl in Et_2O (3.54 mmol/g, 10 ml) to give crystals of 80·HCl (1.7 g, 63.0%). Recrystallization from acetone gave colorless needles, mp 156—157°C. IR ν_{max}^{Nujol} cm^{-1}: 3360—2200, 1730, 1690. NMR (d_6-DMSO) δ: 2.8—3.6 (6H, m), 4.38 (1H, q, J=8 and 4), 7.25 (2H, s), 7.33 (5H, d, J=9), 7.40 (2H, d, J=9), 8.1—8.7 (2H, br), 12.0 (1H, br). *Anal.* Calcd for $C_{18}H_{18}N_2O_3S$: C, 59.58; H, 5.28; N, 7.72. Found: C, 59.43; H, 5.36; N, 7.66.

The starting material used for this method was prepared as follows.

4-[*N*-Phenethyl-*N*-(*p*-toluenesulfonyl)amino]aniline: A mixture of 4-(*p*-toluenesulfonylamino)aniline[9] (13.1 g), 60% NaH in oil (2.64 g) and DMF (150 ml) was stirred at room temperature for 30 min, then phenethyl bromide (11.1 g) was added thereto. The mixture was stirred at 70°C for 2 h, poured into H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to leave an oil, which was chromatographed on silica gel (300 g). Elution with $CHCl_3$ gave crystals of the title compound (13.6 g, 74.6%), mp 105—106°C (from MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3450, 3370, 1335, 1155. NMR δ: 2.43 (3H, s), 2.85 (2H, t, J=7), 3.7—4.0 (4H, m), 6.43 (2H, d, J=9), 6.90 (2H, d, J=9), 7.2—7.8 (9H, m). *Anal.* Calcd for $C_{23}H_{24}N_2O_2S$: C, 68.32; H, 6.46; N, 7.85. Found: C, 69.04; H, 6.60; N, 7.76.

Methyl 3-Chloro-3-[4-[*N*-phenethyl-*N*-(*p*-toluenesulfonyl)amino]phenyl]propionate: $CuCl_2$·2H$_2$O (3.7 ml) and a solution of $NaHSO_3$ (2.64 g) in H_2O (10 ml) were added dropwise to a stirred and ice-cooled solution of 4-[*N*-phenethyl-*N*-(*p*-toluenesulfonyl)amino]aniline (13.7 g) in acetone (150 ml)–MeOH (100 ml) below 5°C. The mixture was stirred at 5°C for 15 min and methyl acrylate (15.0 g) was added thereto. The temperature was raised to 35°C and Cu_2O (0.5 g) was added portionwise to the mixture with vigorous stirring. After N_2 gas evolution had ceased, the mixture was concentrated *in vacuo*, diluted with H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (200 g) with cyclohexane–AcOEt (3 : 1, v/v) to give a pure oil (8.5 g, 99.8%). IR ν_{max}^{neat} cm^{-1}: 1750, 1340, 1155. NMR δ: 2.43 (3H, s), 2.8—4.1 (6H, m), 4.58 (1H, q, J=9 and 4), 7.0—7.7 (13H, m), 9.5 (1H, br s).

5-[4-[*N*-Phenethyl-*N*-(*p*-toluenesulfonyl)amino]benzyl]thiazolidine-2,4-dione: A mixture of 3-chloro-3-[4-[*N*-phenethyl-*N*-(*p*-toluenesulfonyl)amino]phenyl]propionate (9.5 g), thiourea (3.1 g) and ethylene glycol (100 ml) was stirred at 130°C for 16 h, then 1*N* HCl (40 ml) was added. The mixture was refluxed for 5 h, cooled, diluted with H_2O and extracted with Et_2O. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (100 g) with cyclohexane–AcOEt (3 : 1, v/v) to give the title compound as an oil (8.5 g, 67.3%). IR ν_{max}^{neat} cm^{-1}: 3310, 1765, 1705, 1340, 1155. NMR δ: 2.40 (3H, s), 2.8—4.1 (6H, m), 4.58 (1H, q, J=9 and 4), 7.0—7.7 (13H, m), 9.5 (1H, br s).

5-[4-(5-Chloro-2-methoxybenzoylamino)benzyl]thiazolidine-2,4-dione (82): A mixture of 5-chloro-2-methoxybenzoic acid (1.61 g), thionyl chloride (1.73 ml) and C_6H_6 (20 ml) was refluxed for 1 h, then concentrated *in vacuo* to leave an oil. The oil was dissolved in DMF (10 ml) and the solution was added to a solution of 74 (1.9 g) in DMF (10 ml). The mixture was stirred at room temperature for 30 min, diluted with H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated to give crystals of 82 (1.55 g, 48.6%). Recrystallization from MeOH gave colorless prisms, mp 231 – 232°C. IR ν_{max}^{Nujol} cm^{-1}: 3220, 3100, 1740, 1685, 1640. NMR (d_6-DMSO) δ: 3.03 (1H, q, J=14 and 8), 3.40 (1H, q, J=14 and 4), 4.65 (1H, q, J=8 and 4), 7.0—7.8 (7H, m), 10.26 (1H, s), 12.1 (1H, br s). *Anal.* Calcd for $C_{18}H_{15}ClN_2O_5S$: C, 56.22; H, 3.97; N, 7.12. Found: C, 56.30; H, 3.81; N, 7.26.

5-[4-[3-(Pyrrolidinyl)benzoyl]thiazolidine-2,4-dione Hemihydrate (83·1/2H$_2$O): A mixture of 74 (3.84 g), bis(3-chloroethyl)amine hydrochloride (3.8 g) and MeOH (15 ml) was refluxed for 25 h. After removal of the solvent, the residue was partitioned between $CHCl_3$ and sat. aq. $NaHCO_3$. The $CHCl_3$ layer was separated, washed with H_2O, dried ($MgSO_4$) and concentrated. The oily residue was chromatographed on silica gel (100 g) using $CHCl_3$–MeOH (9 : 1, v/v) as an eluent to give crystals of 83. Recrystallization from MeOH gave colorless prisms (0.23 g, 5.3%), mp 231—233°C. IR ν_{max}^{Nujol} cm^{-1}: 1680. NMR (d_6-DMSO) δ: 2.7—3.4

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[1H], m], 4.23 [1F, q, J = 9 and 6], 6.82 [2F, d, J = 9], 7.10 [2H, d, J = 9], 9.0 [1H, br], 12.0 [1H, br]). *Anal.* Calcd for $C_{20}H_{19}N_3O_4S \cdot 1/2H_2O$: C, 58.50; H, 5.06; N, 12.98. Found: C, 58.31; H, 5.39; N, 11.92.

Diethyl 4-(4-Chlorophenoxy)butylmalonate: Diethyl malonate (7.7 g) and a solution of 4-(4-chlorophenoxy)butyl bromide[10] (11.5 g) in EtOH (80 ml) were added dropwise to a stirred solution of Na (1.1 g) in EtOH (80 ml) at room temperature. The mixture was refluxed for 3 h, cooled, diluted with H_2O and extracted with Et_2O. The usual work-up gave an oily residue which was chromatographed on silica gel (150 g). Elution with Et_2O–hexane (1:2, v/v) gave a pure oil (11.2 g, 76.7%). IR ν_{max}^{film} cm^{-1}: 1745, 1725. NMR δ: 1.22 [6H, t, J = 7], 1.5—2.2 [4H, m], 3.33 [1H, t, J = 7], 3.80 [2H, t, J = 5], 4.15 [4H, q, J ~7], 6.63 [2H, d, J = 8], 7.10 [2H, d, J = 8].

Diethyl α-Chloro-α-[4-(4-chlorophenoxy)butyl]malonate: A mixture of diethyl 4-(4-chlorophenoxy)-butylmalonate (10.0 g) and sulfuryl chloride (5 g) was heated at 70°C for 3 h, then concentrated. The residue was dissolved in Et_2O (500 ml). The solution was successively washed with H_2O, sat. aq. $NaHCO_3$ and H_2O, dried ($MgSO_4$) and concentrated to give crystals (9.9 g, 91.7%). Recrystallization from hexane gave colorless needs, mp 31—32°C. IR ν_{max}^{KBr} cm^{-1}: 1740. NMR δ: 1.27 [6H, t, J = 7], 1.6—2.6 [4H, m], 3.39 [1H, t, J = 7], 3.91 [2H, t, J = 6], 4.30 [4H, q, J ~7], 6.70 [2H, d, J = 9], 7.22 [2H, d, J = 9]. *Anal.* Calcd for $C_{19}H_{26}Cl_2O_5$: C, 54.12; H, 6.22. Found: C, 54.20; H, 6.08.

3-Chloro-4-[4-(4-hydroxyphenoxy)butyramido] Acid: A solution of diethyl α-chloro-α-[4-(4-chlorophenoxy)-butyl]-malonate (9.77 g), AcOH (15 ml) and 6 N HCl (15 ml) was refluxed for 20 h, cooled, diluted with H_2O and extracted with CH_2Cl_2. The usual work-up gave 6.6 g crystals (5.0 g, 66.7%). Recrystallization from AcOEt–hexane gave colorless prisms, mp 59—59°C. IR ν_{max}^{KBr} cm^{-1}: 3400, 1745, 1690. NMR δ: 1.8—2.6 [4H, m], 3.75 [2H, t, J = 7], 4.50 [1H, t, J = 7], 6.75 [2H, d, J = 8], 7.35 [2H, d, J = 8], 8.70 [1H, br s]. *Anal.* Calcd for $C_{12}H_{14}ClNO_4S$: C, 52.09; H, 4.71; N, 4.67. Found: C, 52.11; H, 4.82; N, 4.80.

3-Hydroxy-3-(4-phenethyloxybenzyl)succinic Acid: CH_2N_2 (13.5 g) was added to a stirred and ice-cooled mixture of 4-phenethyloxybenzaldehyde[11] (21.2 g), LiCl (4.5 g), KOH (13.2 g), H_2O (64 ml) and dioxane (60 ml). The mixture was stirred at 5°C for 15 h, then at 85°C for 25 h, acidified with 9 N HCl and extracted with Et_2O. The usual work-up gave crystals of the title compound (8.9 g, 79.1%). Recrystallization from AcOEt–hexane gave colorless needles, mp 120—122°C. IR ν_{max}^{KBr} cm^{-1}: 3400, 1745, 1715. NMR δ: 2.97 [2H, t, J = 7], 4.0 [1H, br s], 4.30 [2H, t, J = 7], 6.10 [1H, s], 6.87 [2H, d, J = 8], 7.20 [4H, s], 7.30 [2H, d, J = 8]. *Anal.* Calcd for $C_{20}H_{22}O_6$: C, 70.17; H, 6.48. Found: C, 70.74; H, 6.64.

Methyl 2-Hydroxy-3-(4-phenethyloxyphenyl)acetate: Reaction of 3-hydroxy-3-(4-phenethyloxybenzyl)-succinic acid (3.7 g) and a solution of CH_2N_2 in Et_2O gave the title compound as an oil (3.0 g, quant.). IR ν_{max}^{film} cm^{-1}: 3500, 1740. NMR δ: 3.10 [2H, t, J = 7], 3.63 [1H, d, J = 6], 3.73 [3H, s], 4.30 [2H, t, J = 7], 5.16 [1H, d, J = 3], 6.9—7.4 [9H, m].

Methyl 2-Chloro-3-(4-phenethyloxyphenyl)-acetate (XI): Thionyl chloride (0.22 ml) and pyridine (0.32 ml) were added to a solution of methyl 3-hydroxy-3-(4-phenethyloxyphenyl)-acetate (0.8 g) in CH_2Cl_2 (10 ml). The mixture was stirred at room temperature for 1 h and at 30°C for 30 min, then concentrated in vacuo. The residue was diluted with H_2O and extracted with Et_2O. The usual work-up gave an oily residue, which was chromatographed on silica gel (20 g). Elution with cyclohexane–AcOEt (5:1, v/v) gave XI as an oil (0.36 g, 66.0%). IR ν_{max}^{film} cm^{-1}: 1755. NMR δ: 3.08 [2H, t, J = 6], 3.75 [3H, s], 4.18 [2H, t, J = 6], 5.30 [1H, s], 6.7—7.5 [9H, m].

3-(4-Phenethyloxyphenyl)-thiazolidine-2,4-dione (XII): A mixture of XI (0.66 g), thiourea (0.38 g) and sulfolane (2 ml) was stirred at 110°C for 4 h, then 2 N HCl (3 ml) was added thereto. The mixture was stirred at 100°C for 15 h, diluted with H_2O and extracted with Et_2O. The usual work up gave crystals of XII (0.22 g, 55.0%). Recrystallization from EtOH gave colorless prisms, mp 123—125°C. IR ν_{max}^{KBr} cm^{-1}: 3180, 1765, 1725, 1695. NMR δ: 3.10 [2H, t, J = 8], 4.30 [2H, t, J = 8], 5.33 [1H, s], 6.97 [2H, d, J = 9], 7.31 [2H, d, J = 9], 7.39 [5H, s], 9.0 [1H, br s]. *Anal.* Calcd for $C_{17}H_{15}NO_3S$: C, 66.10; H, 4.81; N, 4.47. Found: C, 65.98; H, 4.89; N, 4.80.

Ethyl 2-Chloro-3-(4-pivaloyloxyphenyl)propionate: A solution of ethyl 3-chloroacetoacetate[12] (1.6 g) in DMF (10 ml) was treated with 60% NaH in oil (0.44 g) and the mixture was stirred at room temperature for 30 min. 4-Pivaloyloxybenzyl bromide[13] (3.1 g) was added to the mixture. The whole was stirred at 70°C for 2 h, poured into ice-H_2O, acidified with 1 N HCl and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was dissolved in EtOH (30 ml), and $Fe(OH)_3$–IH_2O (1.3 g) was added to the stirred and ice-cooled solution. After being stirred for 30 min, the mixture was poured into ice-H_2O and extracted with AcOEt. The extract was washed with H_2O, dried ($MgSO_4$) and concentrated. The residue was chromatographed on silica gel (40 g) using cyclohexane–ice Et_2O (5:1, v/v) as an eluent to give the title compound (3.18 g, 48.8%) as a pure oil. IR ν_{max}^{film} cm^{-1}: 1760, 1670. NMR

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δ: 0.23 (3H, t, J=7), 1.23 (9H, s), 4.12 (1H, q, J=14 and 3), 3.60 (1H, q, J=14 and 7), 4.13 (2H, q, J=7), 4.35 (1H, t, J=7), 7.20 (5H, d, J=2), 7.65 (5H, d, J=9).

Ethyl 2-Chloro-3-(3,4-dimethoxyphenyl)propionate: Reaction of 3,4-dimethoxybenzyl chloride[11] (22.5 g) and 2-chloroacetoacetate[12] (19.2 g) gave the title compound as an oil (13.7 g, 38.9%). IR: ν_{max}^{liq} cm^{-1}: 1740. NMR δ: 1.21 (3H, t, J=7), 3.60 (1H, q, J=14 and 7), 3.39 (2H, q, J=14 and 7), 3.73 (6H, s), 4.15 (2H, q, J=7), 4.27 (1H, t, J=7), 6.68 (2H, s).

2-Chloro-3-(3,4,5-trimethoxyphenyl)propionic Acid: The condensation of 2-chloroacetoacetate[12] (4.33 g) with 3,4,5-trimethoxybenzyl chloride (5.5 g) followed by treatment with 2 N KOH (30 ml) gave the title compound as crystals (6.5 g, 68.9%), mp 98—99°C (from AcOEt–hexane). IR: ν_{max}^{Nujol} cm^{-1}: 1735. NMR δ: 1.37 (3H, t, J=7), 3.60 (3H, t, J=7), 3.42 (2H, t, J=7), 3.68 (3H, q, J=14 and 7), 3.30 (1H, q, J=14 and 7), 3.8—4.4 (6H, m), 4.42 (1H, t, J=7), 6.63 (1H, q), 6.73 (1H, s), 10.56 (1H, s). *Anal.* Calcd for $C_{12}H_{15}ClO_5$: C, 50.97; H, 6.48. Found: C, 50.91; H, 6.70.

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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS, NORTH AMERICA, INC.,

Plaintiffs,

v. 03 CV 8253 (DLC)

MYLAN LABORATORIES, INC and UDL LABORATORIES,

Defendants.

TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS, NORTH AMERICA, INC.,

Plaintiffs,

v. 04 CV 1966 (DLC)

ALPHAPHARM PTY., LTD. and GENPHARM, INC.,

Defendants.

New York, N Y.
January 17, 2006
9:30 a.m.

Before:

HON. DENISE L. COTE,

District Judge

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A. Right.
Q. Right there in the first sentence of the second full paragraph, page 347, second column, right?
A. Right.
Q. It says, "In the rodent, 25 percent of the total brown fat is" – excuse me. I'm going to mispronounce this word.
A. Perirenal.
Q. What is that?
A. Around the kidney.
Q. It says rodent, right?
A. Correct.
Q. And it cites reference 20?
A. Yes.
Q. Did you read reference 20?
A. I did not.
Q. Did you read the title to reference 20?
A. I don't believe I did.
Q. It's right on the next page there.
A. I've read it.
Q. Refers to rats, doesn't it?

A. Sure, yes.
Q. All right. And the authors used rodents in another part of this document, in that same paragraph, the last sentence. See that?
A. Yes, I see that.
Q. They say rodents again, right?
A. Yes.
Q. They cite two references this time. Did you read those references?
A. I did not.
Q. Did you look at the title of those references?
A. I don't believe so.
Q. Those references refer to rats, don't they?
A. Yes.
Q. So when the authors say rodents, they say rats, they mean rats?
A. Not necessarily.
Q. Not necessarily?
A. No.

Q. But they cite the references with rats, discussing rats?
A. But rodents is a general term, and rat's just one animal that's in a rodent.
Q. Now, the article talks about brown fat?
A. Yes, it does.
Q. And thermogenesis?

A. Yes.
Q. Thermogenesis is heat generation, isn't that true?
A. Yes, it is.
Q. And the article talks about cold-induced thermogenesis?
A. Yes.
Q. What is that?
A. I have to see where they talk about it. Do you have that outlined?
Q. Yeah. I believe they talk about it at least in the second column, page 343.
A. That's, it says, "In small mammals, brown fat is a major site of nonsugar and thermogenesis-producing heat in cold exposure," so that's cold-induced thermogenesis.
Q. They also talk about dietary-induced thermogenesis, right?
A. Yes.
Q. What's that?
A. That's dissipating excess calories when overfed.
Q. That's when they eat too much, right?
A. Yes.
Q. You get sweaty?
A. Some people do.
Q. Hot under the collar?
A. I don't know.
Q. Face gets flushed, maybe?
A. Possible.

Q. And heat generation in that manner can play a role in the regulation of body weight, right?
A. Yes.
Q. That makes sense, doesn't it?

A. You're talking about thermogenesis?
Q. Yes. The body generates heat and weight is lost, right?
A. And weight loss?
Q. And weight is lost, right?
A. Yes.
Q. In 1985, according to this article, there was speculation that brown fat in humans may contribute to thermogenesis. That's what it says, right?
A. That's what it says.
Q. So brown fat might be related to the regulation of body weight then, right?
A. Possible, but it was unknown.
Q. All right. Let's turn to page 347. And look at the paragraphs bridging columns 1 and 2. All right? It's actually one paragraph. Sorry. See that paragraph?
A. Which one? I'm -- which paragraph, in column 1?
Q. There's actually a paragraph that's both on column 1 and in column 2.
A. Starts on the bottom of column 1?
Q. Right.
A. Okay.

Q. See that paragraph?
A. Sure.
Q. So some believe that thermogenesis defect may lead to obesity, right?
MR. CONLIN: I object, your Honor.
THE COURT: Sustained.
MR. GOETZ: Okay.
Q. The last sentence in that paragraph talks about speculation. Do you see that?
A. Yes.
Q. What do you understand that to mean?
A. Well, what they're talking about here is there's debate concerning the dietary-induced faculty of thermogenesis in man. So this article, this article basically is studying the thermogenesis, and they want to compare it and see if it's, thermogenesis in man is similar to that that is known in animals. And then they go on to state that there's some doubt if it's actual existence where it suggests there can be

defective in obese man, and some speculated the defect may have been involved brown fat.

So they're talking about a defect in obese man on the effect of brown fat. So --

Q. Sorry.

A. And that it might be somewhat similar to that you see in some genetic strains of rodents.

Q. So they're comparing brown fat in man to brown fat in rodents, right?

A. Well, yes. What they're trying to do is, what they're saying here is we don't know for sure what goes on with the brown fat, is the -- what do I want to say? Does brown fat, is the activity of brown fat in humans correlative to brown fat in rodents, that's what their question is.

Q. That's the speculation they're looking into there in the last sentence, right?

A. That's, that's the way I read this, yes.

Q. And the authors disagreed with that speculation, didn't they?

A. Well, what the authors found was that they didn't find the correlation, and this study, the type of study they did, where they were looking at the mitochondria, and uncoupling of protein in mitochondria which was shown in rodents, they didn't find that in man at, near the activity.

Q. The authors found the brown fat cannot be involved in any genetic defect in humans, right?

A. I don't see, I don't think they conclude that.

Q. Well, you see the last sentence I have up here on the screen, in the second full paragraph on page 347, second column, right?

A. Okay. Where are we at here? I have to find out where we're at.

Q. Sure.

A. Okay. Now, would you ask me the question, please.

Q. The sentence says contrasts, doesn't it?

A. Yes.
Q. Over a hundred?
A. I would suspect.
Q. And some of those -- oh, withdrawn.
Over a period of 28 years or so, is that right?
A. Yes.
Q. And some of those presentations were on papers that you wrote, right?

A. Yes.
Q. You've never given a presentation on the prospective pharmaceutical compound, have you?
A. A presentation on -- oh, boy.
MR. CONLIN: I object. I don't understand the term.
THE COURT: Sustained.
BY MR. GOETZ:
Q. Do you know what a lead compound is?
A. A lead compound is, in this case, would be a compound that they were pursuing to be an antidiabetic drug.
Q. Have you ever given a presentation on how to select a lead compound?
A. I have not.
Q. Have you ever written a paper on that?
A. I have not.
Q. But you have written a few papers, right?
A. Yes.
Q. Over a hundred?
A. Yes.
Q. And some of these published -- were they published papers?
A. Yes.
Q. And some of these published papers were based on the results of toxicological tests, right?
A. Yes.
Q. And you would typically oversee these studies if you're

going to write about them, is that how it works?
A. That's not necessarily true.

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK
----------x
TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS, NORTH AMERICA, INC.,

Plaintiffs,

v. 03 CV 8253 (DLC)

MYLAN LABORATORIES, INC and UDL LABORATORIES,

Defendants.
----------x
TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS, NORTH AMERICA, INC.,

Plaintiffs,

v. 04 CV 1966 (DLC)

ALPHAPHARM PTY., LTD. and GENPHARM, INC.,

Defendants.
----------x

New York, N.Y.
January 24, 2006
9:30 a.m.

Before:

HON. DENISE L. COTE,

District Judge

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I read review articles, for instance, in medicinal chemistry.
Q. Sir, do you recall at your deposition being asked these questions and giving these answers:
"Q. What medicinal chemistry books do you have on your shelf today?
"A. From back then or --
"Q. No, no, any time. Any time. If I walk into your office,

what medicinal chemistry texts do I see?
"A. You'll find a lot of journal stuff with review article type stuffs. I don't really have time to read texts out of my field. So that's what you would find, review articles."
Do you recall that, sir?
MR. VIOLA: Objection.
THE COURT: Overruled.
A. I recall making that statement. And I, what I meant by that was serious reading. If you're asking would I have had a book -- Gilman, for instance, a famous book, in medicinal chemistry, I own Gilman, whether it's on my desk right now, on my bookcase right now. But what that would mean is I would very quickly browse Gilman. I think that's what I would do. But I would read a review article. But Gilman I would just browse.
Q. In response to asking what medicinal chemistry texts you had, you said you didn't have time to read texts out of your field. Are you referring to medicinal chemistry there?
A. Sure, but I have to explain. Read to me means sort of a serious, in-depth experience. Browse means you quickly try to get something, you know, very quickly and it's all a matter of time allocation. So browse, I would do. I certainly had Gilman. Whether I have it today, I'm not sure.
Q. So you're known primarily as a synthetic chemist, is that right?

A. That is true.
Q. Now, you do make some statements in your declaration regarding medicinal chemistry?

A. I do make such statements.
Q. You talked about drug discovery?
A. I did.
Q. Are you familiar with homologation and walking substituents around a ring as techniques in drug discovery?
A. I'm familiar with such language. It's not, it has to be put in a very sharp contextual setting, but I have heard this language used, certainly.
Q. What is a homolog?
A. Technically, a homolog is a substance that differs from its precursor by a CH2 unit.
Q. I see. And if it differs by two CH2 units, is that still a homolog?
A. It would be in the realm of homology. I think the technical -- you want the technical meaning or as the, as what would be used in bantering?
Q. I would like your, your understanding as a synthetic chemist of the meaning of that question.
A. In my judgment, as a synthetic or any chemist for that matter, homolog means the unit of commerce, so to speak, in an organic structure is CH2. So II differs from methyl by CH2. Methyl differs from ethyl by CH2. So an ethyl from propyl by

CH2. So the homolog, if you look at the difference between a precursor structure and its final structure, it would be a CH2. If you're asking if you made two such changes, you would probably be best describing it as a bis homolog or a twofold homolog.
Q. What is an analog?
A. Now, an analog is the more general term, which probably defies precise definition. That's kind of in the eyes of the beholder. It's a structure -- if I had to give you a little more clarification of that, it would be a structure provoked by some other structure. In other words, if you have structure A, it might provoke sort of intellectually the possibility of structure B.
Q. Now, what is homologation?
A. Well, now, the term homologation is, it's a term, I guess technically, in principle, it would be adding a CH2 group to an entity, somehow. Somehow in the system there would be added a

CH2 group.
Q. Well, is it a way of making small changes to try to optimize the balance of toxicity and potency in drug development?
MR. VIOLA: Objection.
THE COURT: Overruled.
A. You're asking is that the primary purpose of homologation?
Q. Is homologation a way of making such small changes, to

optimize?
MR. VIOLA: Objection.
THE COURT: Overruled.
A. Homologation is a way of making small changes. The purpose of doing the homologation would be very context driven. It may be a small change, it may be a very large change in consequence. Homologation may have profound changes. It may have small changes. But homologation, you're asking me as a chemist, and a scientist, homologation is the act of expanding a structure by a CH2 group, somewhere.
Q. Right. And that would be to optimize the --
A. That's something separate. That's something you may or may not have at your purpose for homologation.
Q. Sir, I'm going to ask you again about your deposition page 98, lines 15 to 22.
A. Do I have that here?
Q. Would you like to get a copy?
A. Yeah. What was the page number?
Q. Page 98. And the lines are 15 to 22 -- I'm sorry. 14 to 22.
A. Right.
Q. Now, were you asked these questions and did you give these answers:
"Q. Before you get to the homologation stage that you talked about, let's assume --

"A. Actually, I don't remember talking about that as a desirable way to go. I said one would make small changes to

optimize, but it may be homologation.
"Q. Homologation would be one way of making the small changes?
"A. In principle."
Do you see that.
A. I do.
MR. VIOLA: Objection.
THE COURT: Sustained. Stricken.
BY MR. HOVDEN:
Q. Do you agree, Doctor, that homologation is one way of making small changes to optimize the properties of a molecule?
A. Well --
MR. VIOLA: Objection.
A. I have trouble --
THE COURT: Overruled.
A. I have trouble understanding the question. Homologation is a straightforward term. It means to expand a structure by unit. That's what it means scientifically. Now, why one does that, that's some, that's not the only reason to do homologation. It's one of different reasons, a menu of reasons. So, I'm afraid you're getting me to, we're confusing, the sum of you and me are confusing motive with act. Act of homologation is to add a CH2 group. It's as simple as that. Now, why one does that? There could be a menu of reasons for

doing that. So I'd like to know exactly what the thrust of your question is.
Q. Let me ask you this question, Doctor. If one wants to optimize the properties of a molecule, is homologation one technique that can be used to accomplish that?
A. It's a very context -- is it one of many possibilities? It is one of many possibilities.
Q. And homologation is a pretty standard technique in medicinal chemistry, isn't that right?
A. I wouldn't concede that point. It's not a matter of my conceding; I don't see it that way. It's very much dependent on the context of the situation as to whether it's something that you would do.
Q. Well, is it your understanding, your understanding is medicinal chemistry is a science?
A. I do.

Q. And as such, you would expect it to have some principles, right?
A. Sure. There are guiding, there are, let's say, protocols that are followed.
Q. And techniques?
A. There are strategies and techniques.
Q. Textbooks and courses, right?
A. Certainly.
Q. And would you expect that in textbooks in the early 1980s,

that homologation would be taught as a technique?
A. Truth of the matter is, I don't remember it as being described as a technique. It is one of many acts that people might undertake in the hope of improving a structure. But is it something that every schoolboy would be taught, that's what you do, start homologizing, I don't think that's right. I don't think that's correct.
Q. My question, Doctor, is medicinal chemistry textbooks of the early '80s, would you expect homologation to be taught in those textbooks?
A. It would appear in there, but I would not expect it to be taught as sort of the way to go.
Q. Ring walking, Doctor, what is that?
A. Ring walking?
Q. Yeah.
A. Well, I take it it means, if you have a certain ring which you regard in your mind as a fixed matrix, which is not going to change, then, and you have a particular substituent on the ring, that term would imply perhaps the movement of that substituent somewhere in that ring.
Q. In the materials you reviewed for this case, did you see any examples of ring walking of substituents?
A. I remember that term or something very close to that term appearing in, for instance, the Mosberg report.
Q. And, in fact, in I think paragraph 129 of your declaration,

you admit that Takeda didn't invent the technique, is that

right?
A. I could tell you that without looking. They did not invent the technique --
Q. Okay.
A. -- of changing the position of substituents.
Q. That was another standard technique as of the early 1980s, is that right?
A. Standard and context that would require elaboration on my part. Was it out there? Yes. Was it practiced? Only in certain situations.
Q. Now, Doctor, when you reviewed the -- are you familiar with the Sohda article?
A. Yes.
Q. And that's PTX76, I believe.
THE COURT: Could you spell that?
MR. HOVDEN: S-O-H-D-A.
THE COURT: Oh.
MR. HOVDEN: Maybe it's my Midwestern accent.
THE COURT: Well, I'm a Midwesterner. I thought you said Selig.
MR. HOVDEN: Sorry, your Honor.
THE COURT: No. Thank you.
BY MR. HOVDEN:
Q. At one point, Doctor, you systematically went through the

ethyl and methyl substituents on the phenyl ring, is that right?
A. There were --
MR. VIOLA: Objection.
THE COURT: Sustained.
BY MR. HOVDEN:
Q. Doctor, at any point, did you review, in particular, the ethyl and methyl substituents on the phenyl ring in the Sohda article?
A. I certainly looked at them.
Q. Right.
A. Took note of them.
Q. And, in fact, what you're reviewing is reviewing the results of homologation and ring walking, is that right?
A. I look at many aspects in Sohda, including changes of whole

MR. BROWN: I believe that that will take care of most of the issues.

THE COURT: Okay.

MR. BROWN: One other matter, in order to expedite things. There are four Alphapharm trial exhibits that we intend to offer during the examination of these two witnesses. And I just discussed it with plaintiffs' counsel, and they have no objections.

THE COURT: And they are.

MR. BROWN: Alphapharm Trial Exhibit 224.

THE COURT: 224 is received.

(Defendant's Exhibit Alphapharm 224 received in evidence)

MR. BROWN: 217.

THE COURT: 217's received.

(Defendant's Exhibit Alphapharm 217 received in evidence)

MR. BROWN: 226.

THE COURT: 226 is received.

(Defendant's Exhibit Alphapharm 226 received in evidence)

MR. BROWN: And 219.

THE COURT: And when I said those numbers, I should have in each instance said Alphapharm. So it's Alphapharm 217, 219, 224, and 226 that are received.

(Defendant's Exhibit Alphapharm 219 received in evidence)

MR. MURPHY: Your Honor, there's one more, it's Alphapharm 233, which is also not objected to.

THE COURT: It's received.

(Defendant's Exhibit Alphapharm 233 received in evidence)

THE COURT: Dr. Colca.

GERARD COLCA,

called as a witness by the Plaintiffs,

having been duly sworn, testified as follows:

THE COURT: I believe you're being given a copy of your trial declaration which is Exhibit --

MR. VIOLA: 430.

THE COURT: Did you read that carefully before signing it?

THE WITNESS: Yes.

THE COURT: Do you swear to the truth of its contents?

THE WITNESS: Yes, I do.

THE COURT: Any objections?

430 is received.

(Plaintiffs' Exhibit 430 received in evidence)

MR. VIOLA: Your Honor, at this time we'd like to move in the associated Takeda trial exhibits, 107, 109, 111, 113, 115, and 359.

MR. DiLELLO: Your Honor, regarding 359, I'm going to be cross-examining Dr. Colca about that. And would I be permitted to reserve an objection? Depending what comes out of my examination, I may move to strike it.

THE COURT: That's fine. It will, all of these exhibits are received. Exhibit 359 is received subject to potentially being struck if there is an objection as we go along.

(Plaintiffs' Exhibits 107, 109, 111, 113, 115, and 359 received in evidence)

CROSS-EXAMINATION

BY MR. BROWN:

Q. Good afternoon, Dr. Colca.

A. Good afternoon.

Q. I'd like to start by focusing on paragraph 31 of your trial declaration that's in front of you. And in this paragraph, you mentioned four particular toxicities that you primarily focused on in the screening tests for a successor compound to ciglitazone. Is that correct?

A. I think so. Should I read it?

Q. Please, to yourself.

A. Okay. I recall now.

Q. And those four are eye lens, heart, liver, and red blood cells, correct?

A. That's correct.

Q. You don't mention weight gain as a toxicity measure that you've used in the screening, and I wanted to ask you, in the 1983-1984 time frame, weight gain in diabetic animals, in an animal model was not something that would warrant the Upjohn researchers off of studying a particular thiazolidinedione, is it?

A. They would not, that's correct.

Q. Isn't that because weight gain in diabetic animals in those tests is caused partly by the fact that without treatment, the animals are dumping a lot of calories in their urine and the drug you're testing fixes that?

A. That is correct.

Q. And the animal continues to eat as much as usual, but without dumping the calories in the urine, it predictably gains weight?

A. That's correct.

Q. And, in fact, Doctor, this phenomenon of weight gain in animal models was observed by Takeda and Upjohn in 1983 or 1984 with ciglitazone, correct?

A. Yes. It depends on the animal model, but in some animal models. I should say not everybody felt the same way. That's what I felt, is that the weight gain was part of the pharmacology.

Q. You also don't focus on something called brown fat or brown adipose tissue in the toxicities you used to screen. Why is

that?

A. I don't know why we should.

Q. Upjohn was never warned away from continuing the development of any of the thiazolidinediones because of brown fat or brown adipose tissue, was it?

A. I didn't consider it a problem, no.

Q. In fact, some people thought it was a positive, didn't they?

A. That's correct.

Q. Dr. Colca, in paragraph 42 of your trial declaration, you

detailed the methodology for a four-day test that Upjohn performed on KKA yellow mice for blood glucose and, blood glucose lowering and triglyceride lowering, and I'd like you to just review that paragraph and confirm for me that that's the case.
A. That's correct.
Q. And in here, you discuss Upjohn's standard protocol for these types of tests, is that correct?
A. Yes.
Q. You state, "We began by carefully matching a pool of animals by age, body weight, and nonfasting blood glucose." Is that correct?
A. That's correct.
Q. Why did you carefully match the animals by nonfasting blood glucose?

A. These animals have a range of glucose levels, and so if you were to pick a group without matching them, you might run the risk that one particular group would be lower than the other. And that will make it then harder to show differences. You could be so unlucky as to have animals with all the lowest glucose end up in the control group, for example.
Q. Why did you carefully match the animals by body weight?
A. Well, we're, we want to match the doses as well. And so, the closer they are in match to body weight, the doses are going to be more similar too.
Q. You would ultimately normalize the body weights, is that correct?
A. The results should do, but the amount of drug the animal gets will be dependent on the amount of food that he eats.
Q. Doctor, why did you carefully match the animals by age?
A. Well, generally, they were all about the same age in this particular case. You want to match the groups for all the parameters you could think of to be as close as possible.
Q. Why did you single out age here, or --
MR. VIOLA: Objection.
Q. -- among two other parameters you tested?
THE COURT: Overruled
A. Well, age would be one of the components.
Q. In paragraph 56 of your trial declaration, you discuss

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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS, NORTH AMERICA, INC.,

Plaintiffs,

v. 03 CV 8253 (DLC)

MYLAN LABORATORIES, INC and UDL LABORATORIES,

Defendants.

TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS, NORTH AMERICA, INC.,

Plaintiffs,

v. 04 CV 1966 (DLC)

ALPHAPHARM PTY , LTD. and GENPHARM, INC.,

Defendants.

New York, N.Y.
January 25, 2006
9:30 a.m.

Before:

HON. DENISE L. COTE,

District Judge

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because it sounded like you're asking me about four different questions at once.
Q. What I'm asking you is that in 1984, isn't it your belief that someone pursuing a promising lead would start with a molecule that demonstrates desirable efficacy and safety

properties and then try to find a better compound by investigating the structure-activity relationship around that molecule?
MR. VIOLA: Objection.
THE COURT: On what ground?
MR. VIOLA: They've objected to this witness as not being an expert, and he's just asking him his belief about what someone else would do in 1984.
THE COURT: Okay. I've understood these questions to be rooted in this witness' experience in 1984 in his development of pioglitazone. Is that your intention, counsel?
MR. BROWN: Yes, it is.
THE COURT: Okay. So I'll ask you to restate the question so that's clear.
BY MR. BROWN:
Q. In 1984, when you were pursuing a promising lead, was it your practice to start with the molecule that demonstrates desirable efficacy and safety properties and try to find a better compound by investigating the structure-activity relationship around that molecule?
A. In general, yes.
Q. And the goal of that was to try to determine what the optimal molecule would be?
A. The reason I'm hesitating is that it's not always possible to find the optimal molecule, but to find a molecule that

satisfied minimally acceptable criteria for development.
Q. In your experience, was that process of optimizing the properties of the molecule by structure-activity relationship the classic approach in medicinal chemistry in 1984?
MR. VIOLA: Objection.

THE COURT: Well, I'm happy to let you ask this witness this question, but it entirely undercuts objections, certain objections to his testimony. Go ahead.

I just want to advise you, you have about five minutes left.

THE WITNESS: Can you restate the question, please?

BY MR. BROWN:

Q. Doctor, isn't that process, namely, optimizing the properties of the molecule, the structure-activity relationship, the classic approach in medicinal chemistry in 1984?

A. It was a major approach in 1984.

Q. I'd like to go to Plaintiffs' Trial Exhibit 83.

MR. BROWN: And could we have the slide on that.

Q. It's tab 6 of your binder, I believe, and page 3 of that. And you've seen this document before, Doctor, is that correct?

A. Yes, I have.

Q. And we've just, we've prepared a version for the screen that just takes out the black and condenses them all together. And in this document, could you confirm for me that the portion

of the molecule that's being kept the same is shown at the top of the page? Is that correct?

THE COURT: Which exhibit -- I know it's 83, but what is this --

MR. BROWN: This is the A1534 report.

THE COURT: Thank you.

A. Well, the R isn't being kept the same, obviously, but the thiazolidinedione methyl phenyl ring is.

Q. And down the side of the page, the other portions of the molecule are being modified and altered to determine what impact structure has on activity, is that correct?

MR. VIOLA: Objection.

THE COURT: Sustained.

BY MR. BROWN:

Q. Dr. Morton, you are familiar with the toxicity testing that would be used by Upjohn management when considering whether to enter pioglitazone into the Upjohn development system, is that correct?

A. Yes, I was familiar.

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S. 59年 1 月 月報

名川主務 研究所長	提出日 S. 59. 1. 10

担当責任者： 藤田 剛	担当者（主研以上）： 松原 藤田

題　　名：抗血栓性薬剤の研究（1）（精原病に於ける）

(1) ADD-3195 構造化合物：予備毒性試験より急性毒性化合物について要約及び比較検討中。AD-4933≒AD-4974≒ADD-3195 >> ADD-3197 の順に強く、長期投与は ADD-3195 より弱く、ADD-3197 はほぼ同等の強さである。

[redacted]

(2) 有機合成を担当：ADD-3197 ラットのプロコンバリン刺激性インスリン分泌亢進作用をもつ インアルテルノリンなる性質と一緒に検討中

テーマ名（担当者）	特記事項（進捗状況・今後の方針等）	コメント・指示事項等
藤田	① ヒポスリージアン：凡検定より有効に作用した。	
	[redacted]	
	③ ADD-3195 構造化合物：予備毒性試験より急性毒性化合物の要約及び比較検討中。即ち AD-4933≒AD-4974≒ADD-3195 >> ADD-3197 の順に強く、長期投与は ADD-3195 より弱く、ADD-3197 はほぼ同等の強さである。	AD-4933 を第一候補として、ADD-3195 との要約書比較を検討する。
松原	④ 有機合成を担当：AD-3195 ラットのプロコンバリン(2%)に対するインスリン分泌亢進をする。 ⑤ ヒポスリージアン：ラットには高脂肪食で高血糖症より高血糖の予防を示した。 ⑥ ADD-3195 の投与を新薬担当への依頼：pain-free ラットに、高脂肪(10%, 20%)に於いても強く優れた血糖上昇抑制の効果を示した。	

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((Confidential)) (Form II)

January 1984 Monthly Report

Biology Lab Director Nagawa	Date of submission: 1/10/1984

Person responsible: Takeshi Fujita {seal: Fujita}	Persons assigned (Persons above the Chief Researcher level): Matsuo, Fujita

Summary: Study on metabolizing drugs (1) (diabetes treatment drug)
(1) ADD-3959 peripheral compounds: 4 compounds selected from the preliminary toxicity test were compared for their strength in drug efficacy and thoroughly examined. They were weak in this order: AD-4833 ≈ AD-4874 ≈ ADD-3894 >> ADD-3907, the first three samples exhibited about 5 times the strength of ADD-3878, and ADD-3907 exhibited nearly the same strength.

[Redacted]

(3) Non-obese type II diabetic model: Currently accumulating basic data on isopreterenol's reactivity to glucose-stimulating insulin secretion reaction in N-STZ rats, etc.

Name of theme (person assigned)	Special remarks (progress status, future policy, etc.	Comments, instructions, etc.
Fujita	(1) Primary screening: Effect was recognizable in 3 out of 16 samples. [Redacted] (3) ADD-peripheral compounds: Using KKA^y mice and SD rats, the efficacy strength of the 4 compounds selected from the preliminary toxicity test were thoroughly examined in terms of the blood glucose, NEFA, and TG lowering effects. AD-4833 ≈ AD-4874 ≈ ADD-3894 >> ADD-3907. The first three samples exhibited about 5 times the strength of ADD-3878, and ADD-3907 exhibited an equivalent strength.	Select AD-4833 as the first candidate, and study drug efficacy and toxicity comparison with ADD-3959.
Matsuo	(4) Non-obese type II diabetic model: N-STZ-1.5 and N-STZ-5 rats did not show an insulin secretion reaction to isopreterenol (iv). (5) Wistar fatty rats: In female rats, the high-starch diet caused the onset of hyperglycemia more frequently than did the high-sucrose diet (6) Effect of ADD-3959 on brown adipose tissue: direct effect on brown adipose tissue and weight increase was confirmed in pair-fed rats treated with a high dose (300 mg/kg, 2 wk) as well.	

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Certification

I, Sharon E. Nothman, do hereby certify the following:
I am fluent in the English and Japanese languages. I have translated and/or reviewed the translation of the Japanese document identified as:

TAK-00003970-39721L

and find it to be a true and accurate translation to the best of my knowledge and ability.

I affirm under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Signature: Sharon Nothman

Date: Aug 18, 2005

Sharon E. Nothman, President
Kotoba, Inc.
8417 Fenway Road
Bethesda, MD 20817

SA93

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Alphapharm Pty, Ltd.
Genpharm, Inc.

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

Takeda Chemical Industries, Ltd. and Takeda Pharmaceuticals North America, Inc Plaintiffs, v. Alphapharm Pty, Ltd., et al. Mylan Laboratories, Inc., et al. Watson Pharmaceuticals, Inc., et al. Ranbaxy Laboratories, Ltd., et al. Defendants.	(CONSOLIDATED) Civ. Action No. 04-CV-1966(DC)

DECLARATION OF HENRY I. MOSBERG

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I, Henry I. Mosberg, of full age, declare pursuant to 28 U.S.C. § 1746 that:

1. I have been retained as an expert consultant to the law firm of Frommer, Lawrence and Haug, LLP, to provide an expert opinion in this matter on the question of whether the compound known as pioglitazone was obvious to those skilled in the art prior to the date Takeda filed its patent application specifically covering this compound. Takeda's pioglitazone patent issued as United States patent 4,486,777. I will refer to this patent throughout this trial declaration as the '777 patent. I have been asked to provide the Court with this declaration in lieu of my testimony on direct examination.

QUALIFICATIONS

2. I am an expert in the field of medicinal chemistry, and can provide testimony that will assist the Court in rendering a verdict on what persons of ordinary skill in the art of medicinal chemistry would do had they reviewed the relevant prior art in this matter. The bases for my qualifications as an expert are set forth as follows:

a. **Education:** I received my B.S. in Chemistry from the University of Illinois, Chicago in 1971 and my Ph.D. in Biophysical Chemistry from the University of Illinois, Urbana in 1976. Biophysical chemistry is an interdisciplinary field which aims to rigorously quantify the physical and chemical principles governing biological systems.

b. **Academic Duties:** I joined the faculty of the University of Michigan, Department of Medicinal Chemistry in 1983 and have held the rank of Professor there since 1995. The field of medicinal chemistry is a subset of Chemistry and seeks to uncover the precise chemical mechanisms of action in animals which ultimately lead to the development of useful pharmaceutical agents, principally for human beings. Since 1999, I have served as Associate Dean of Research and Graduate Education where some of my responsibilities are promoting and

facilitating external funding opportunities, overseeing internal funding mechanisms, and allocating research space. I have served on the Medicinal Chemistry Program Committee at the University of Michigan since 1986. The Committee addresses the graduate curriculum and degree requirements in Medicinal Chemistry. As either an assistant or full Professor at the University of Michigan, I have taught numerous undergraduate and graduate courses dealing with medicinal chemistry concepts, drug design and "lead optimization." Lead optimization is the method by which medicinal chemists slightly modify or "tweak" the structures of a promising chemical compound, known as a "lead," to maximize its potency and/or minimize toxicity or unwanted side effects. Drug synthesis is the method by which those structural changes are made to the lead.

c. **Publications:** I have authored or co-authored 142 peer-reviewed articles relating to the issues of drug design, including lead optimization, drug synthesis, and drug mechanism of action. The specific articles I have authored or co-authored are set forth in my up-to-date curriculum vitae, Alphapharm Trial Exhibit 14 (Exhibit A to this Declaration). The articles appear on pages 4 through 14 therein.

d. **Awards:** In 2005, I was awarded fellowship status with the American Association for the Advancement of Science (AAAS), the world's largest general scientific organization. Fellowships in AAAS are highly competitive, and are only awarded to a select few within a discipline once a year. In 1989, I was awarded a NIDA Research Scientist Development Award in support of research toward understanding the structural requirements for selective opioid compounds. In 1973 and 1977, I received pre-doctoral and post-doctoral fellowships respectively with the National Institute of Health (NIH), one of the world's foremost medical research organizations. My pre-doctoral fellowship concerned NMR studies of the mechanism

of the enzyme aspartate transcarbamylase. My post-doctoral fellowship concerned metal binding properties of the peptide antibiotic, bacitracin A.

e. **Editorial Boards:** I presently serve on the editorial boards of two journals, *Biopolymers-Peptide Science* and *The Journal of Peptide Research*, and have recently completed a four year term on the editorial board of the *Journal of Medicinal Chemistry*. On those editorial boards, I have provided, and continue to provide, "peer review," that is, I review submitted manuscripts to determine whether the science supporting them is valid, complete, and merits publication in the journal. Articles lacking in adequate support are rejected. I am a Senior Associate Editor of the new journal, *Chemical Biology & Drug Design*, which will launch in 2006. In this capacity I will be making higher-level editorial and content decisions with authors, in addition to coordinating with other peer-reviewers for the proposed articles. I also serve as an ad hoc reviewer for organizations such as NIH, the National Science Foundation, the Medical Research Council of Canada, Research Corporation, the Science Foundation of Ireland, and the Human Frontier Research Fund.

f. **Specific Drug Design Experience:** I have specifically engaged in the process of drug design and lead optimization on at least 10 different compounds, including the investigation of structure-function relationships of several opioid peptides and non-peptides, the development of inhibitors of RGS protein-mediated termination of G protein activation (with potential as a novel class of drugs), and the development of peptide inhibitors of platelet activation, with potential value for prevention of heart attacks and strokes. Peptides are a chain of amino acids which serve critical biological functions. Insulin, used naturally in the body to lower blood glucose, and used for the specific treatment of diabetes, is one of a vast array of biologically important peptides. Over the years, I have been awarded extramural grants by NIH

and other agencies for all of this work. The currently active NIH research grants on which I am the principal investigator or co-principal investigator are set forth in page 3 of Alphapharm Trial Exhibit 14 (Ex. A to his Declaration). My work has resulted in three issued patents covering the optimized peptide compounds, and a pending application covering a fourth such compound.

g. **Previous Certification as an Expert:** I was accepted as an expert in medicinal chemistry in the United States District Court for the District of Massachusetts in September, 2005. I provided the court there with an expert tutorial in medicinal chemistry. The case in which I testified is known as *Aventis Pharma Deutschland Gmbh and King Pharmaceutical v. Cobalt Pharmaceuticals, Inc.*

METHOD AND DOCUMENTS REVIEWED

3. The '777 patent (Alphapharm Trial Exhibit 7, attached to this Declaration as Exhibit B) is directed to thiazolidine derivatives of a particular formula which "exhibit in mammals blood sugar- and lipid-lowering activity, and are of value as a therapeutic agent for treatment of diabetes and hyperlipidemia." (Alphapharm Trial Exhibit 7, Preamble) Prior art references within, and reasonably pertinent to, this field of endeavor were relevant to me on the question of whether a person of ordinary skill would have found the pioglitazone compound obvious in light of this art.

4. I was made aware that Takeda employees, years before the '777 patent was applied for, published the results of studies they had conducted on thiazolidine derivatives with anti-diabetic properties, such as lipid and blood glucose-lowering effects. I was also made aware that Takeda's inventors sought and received several issued patents concerning the same subject matter. I requested that Frommer Lawrence and Haug provide all of those publications, patents and publicly-available prosecution histories to me. I also requested the '777 patent itself, the application for which was filed on January 17, 1986.

5. I received from Frommer Lawrence and Haug a packet of prior art materials that included the following:

a. United States Patent 4,287,200 (the "'200 patent"), issued in the United States on September 1, 1981 and assigned to Takeda Chemical Industries, Ltd. (Alphapharm Trial Exhibit 1 [Exhibit C, attached)];

b. Application No. 62,512, the Prosecution History associated with the '200 patent, the application for which was filed on July 27, 1979 (Alphapharm Trial Exhibit 2 [Exhibit D, attached)];

c. Sohda, T. et al., "Studies on Antidiabetic Agents. II.1 Synthesis of 5-[4-(1-Methylcyclohexylmethoxy)-benzyl]thiazolidine-2,4-dione (ADD-3878) and Its Derivatives," *Chemical and Pharmaceutical Bulletin* 30:10 (October, 1982) 3580-3600 (Alphapharm Exhibit Alphapharm Trial Exhibit 3 [Exhibit E, attached)].

d. United States Patent No. 4,340,605 issued in the United States on July 20, 1982 and assigned to Takeda Chemical Industries, Ltd. (Alphapharm Trial Exhibit 4 [Exhibit F, attached)];

e. United States Patent No. 4,444,779, issued in the United States on April 24, 1984 and assigned to Takeda Chemical Industries, Ltd. (Alphapharm Trial Exhibit 5) [Exhibit G, attached];

f. Application No. 476,017, the Prosecution History associated with the '779 patent, the application for which was filed on March 15, 1983 (Alphapharm Trial Exhibit 6 [Exhibit H, attached]).

Alphapharm trial exhibits 1 through 6 all concern thiazolidine derivatives with anti-diabetic properties, such as lipid and blood glucose-lowering effects. Each describes and/or teaches thiazolidine derivatives with structures more or less similar to pioglitazone. The '200 (Alphapharm Trial Exhibit 1), '605 (Alphapharm Trial Exhibit 3) and '779 (Alphapharm Trial Exhibit 5) patents and their respective prosecution histories all set forth the activities of the United States Patent Office, an agency of the United States government. In addition to its appearance in the prior art and my reliance on it for my opinions, the Sohda article (Alphapharm

Trial Exhibit 2), noted in 6c. above, was published in what I know is a reliable periodical relating to chemistry and pharmaceutical science.

6. Other than the prior art listed above, I also received from Frommer Lawrence and Haug the following documents relevant to my inquiry:

a. the '777 patent (Alphapharm Trial Exhibit 7) [Exhibit B, attached];

b. a letter from Frommer Lawrence and Haug attorney Kevin Murphy to Barbara Moore, litigation counsel to Takeda, dated July 8, 2005 (Alphapharm Trial Exhibit 8) [Exhibit I, attached];

c. portions of the transcript of Takeda employee Hiroyuki Odaka, dated March 24, 2005 ("Odaka Deposition," Alphapharm Trial Exhibit 9) [Exhibit J, attached];

d. an article by, Cunningham, S. et al., entitled "The Characterization and Energetic Potential of Brown Adipose Tissue on Man," *Clinical Science* 69 (1985) 343-348 (Alphapharm Trial Exhibit 10) [Exhibit K, attached]; and

e. the results of Takeda's drug design work on structural analogs to pioglitazone found in Fujita, T., "Pharmacological Actions of Selected Compounds in Normal and Diabetic Animals," Takeda Biology Laboratories, January 1984 (Alphapharm Trial Exhibit 11) [Exhibit L, attached].

7. The '777 patent, like the other patents above, sets forth the activities of the United States Patent Office. It covers formulas of the compound of interest. Broadly, these compounds are what I would term ethylated pyridyl thiazolidine derivatives. The letter from Frommer Lawrence and Haug detailed for me that Takeda only claimed that Alphapharm infringed claims 1, 2 and 5 of the '777 patent, so I confined my obviousness analysis to those claims. I am familiar with the signature of Kevin Murphy and his signature appears on the signature line of Alphapharm Trial Exhibit 8. I used Alphapharm Trial Exhibit 10, the Cunningham article, to educate myself about how persons of ordinary skill would respond to brown fat results in the 1980s. That article was published in *Clinical Science*, a well-recognized and reliable journal

relating to health and disease. I similarly reviewed Takeda's actual drug design work in Alphapharm Trial Exhibit 11 as a check on my analysis of what others of skill in the art would do. Alphapharm Trial Exhibit 11 represents statements made by Takeda's scientist, Takeshi Fujita, concerning the scope of Takeda's drug development, made while Dr. Fujita was employed by Takeda. As a drug developer for Takeda, Dr. Fujita's report was made within the scope of his employment.

8. To further educate myself, I performed my own research on what persons of ordinary skill in the art were doing in the field of drug design at or before the time of Takeda's alleged invention. That research uncovered the following article:

- Nohara, A. et al., "Studies on Antianaphylactic Agents. 6.1 Synthesis of Some Metabolites of 6-Ethyl-3(1H-tetrazol-5-yl)chromone and their Analogues," *Journal of Medicinal Chemistry* 22:3 (1979) 290-295 (Alphapharm Trial Exhibit 12) [Exhibit M, attached].

This article detailed that persons of ordinary skill in the art—including Takeda—had practiced the synthesis of routine homologues to improve promising drug compounds. Had the same method been applied to the lead compound that emerged from the prior art, it would have led naturally to the relevant formulas claimed in the '777 patent. I relied on these articles as prior art as well as background, and can attest that the *Journal of Medicinal Chemistry* is a well-recognized, reliable periodical concerning medicinal chemistry.

9. Persons of Ordinary Skill in the Art: I endeavored to analyze the prior art—not from my own considerable experience as a medicinal chemist—but from the standard of a person of *ordinary* skill in the art. On this issue, I looked carefully at what the above patents covered, the issues involved in synthesizing experimental pharmaceutical compounds generally, and the average educational level of drug developers. The person of ordinary skill for the art presented in this case would generally have a combination of training and experience. For example, a

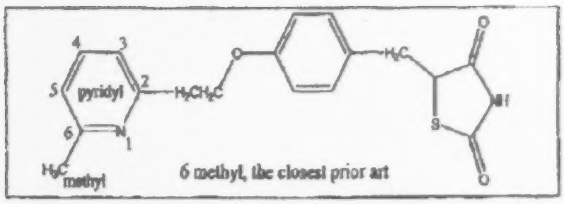
typical person of ordinary skill in this art would have secured her Ph.D. in medicinal chemistry or a related field, done postdoctoral work for two to three years and thereafter secured a position with a pharmaceutical company. After two or three years there, she would have achieved the necessary training and experience to qualify as a person of ordinary skill.

OPINION

10. I was retained as an expert in June 2005 in this matter. As I noted above, my task was to determine whether persons of ordinary skill in the art of medicinal chemistry would, after reviewing the available prior art before Takeda filed the '777 patent application, be led naturally to the pioglitazone compound with minimal experimentation. After my review of this art—and in particular, the early publication of a close structural analog to pioglitazone—it is my considered opinion that Takeda did not invent anything in the '777 patent. Persons of ordinary skill in the art would have recognized as early as 1982—nearly 4 years before Takeda filed its application—the very real promise of this close structural analog, and performed the few and quite routine experiments in drug design necessary to "tweak" it and reach the invention. Persons of ordinary skill would have undertaken this task with a reasonable expectation of success.

Pioglitazone Is Structurally Similar to the Lead Prior Art Compound

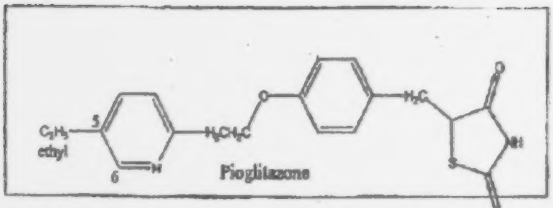
11. In my review of the prior art, I noted that as early as September 1, 1981, Takeda disclosed in Alphapharm Trial Exhibit 1[C, attached], the '200 patent, a compound it called a "novel thiazolidine derivative having hypolipidemic [i.e, lipid-lowering] and hypolglycemic [sic, i.e., blood-glucose lowering] activities with low toxicity." Alphapharm Trial Exhibit 1, col. 1, lines 4-6. The compound appears in Alphapharm Trial Exhibit 1 at column 13 and is listed as compound 42. That compound is known as a 2 "pyridylmethyl" with a "methyl" at the 6 position on the "pyridyl" ring. Compound 42 has this structure:



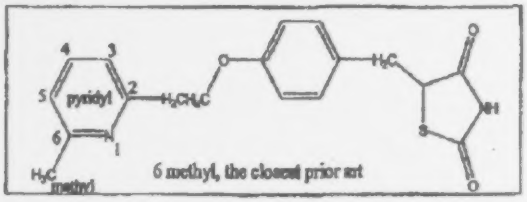
6 methyl, the closest prior art

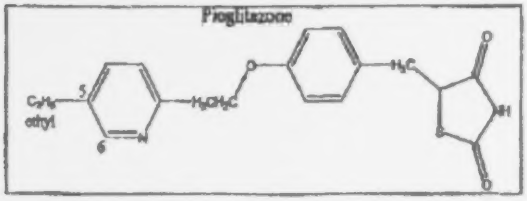
12. I have set forth in red the left-most portion of compound 42, which I will call the left-most "moiety." A moiety is a portion of the molecule of interest. Despite the color-change, the above diagram is a full and accurate depiction of the compound disclosed as compound 42 in the '200 patent. The left-most moiety consists of a "pyridyl" ring with a "methyl substituent" at position 6. "Pyridyl" denotes a planar six-membered ring of 5 carbon atoms and one nitrogen atom. Because carbon atoms are so common in organic chemistry, they are often represented by mere points of intersection, rather than the letter "C", where they appear. For ease of reference, any moiety attached to a ring, known as a "substituent," is given a particular number corresponding to the position on the ring to which it is attached. Chemists start numbering the ring's positions with the highest atomic weight atom in the ring. In this instance, nitrogen bears a higher atomic weight than carbon, and thus would be numbered "1." In the example above, numbering proceeds in counterclockwise fashion so that the 2 position has the CH_2CH_2O substituent. Thus—following that pattern– the CH_3 substituent, known as a "methyl," in the location above is called a 6 methyl. Because this compound is so similar to pioglitazone, I will refer to it from here on simply as the "6 methyl."

13. The compound known as pioglitazone, which Takeda first claims in the '777 patent, has a very similar chemical structure to the earlier-disclosed 6 methyl. Indeed, it is an analog of the closest prior art. Pioglitazone has the formula:



Pioglitazone is claimed in dependent claim 2 of the '777 patent, Alphapharm Trial Exhibit 7. There are only two differences between pioglitazone and the 6 methyl. Takeda substituted an ethyl (C_2H_5) for the methyl (CH_3) and linked that substituent at the *5* position instead of the 6 position, as shown below:





Claims 1 and 5 of the '777 patent are even closer to the prior art 6 methyl compound because they both claim the ethyl (C_2H_5) at *any* position, including the 6 position. Alphapharm Trial Exhibit 7, claim 1. Notably, claim 4 of the '777 patent (not at issue here), in fact, specifically claims the ethyl (C_2H_5) at the 6 position.

14. Moreover, Takeda admitted that pioglitazone is structurally "similar" to other methyl substituents at the 3, 4 and 5 positions on the pyridyl ring in the '777 patent. Alphapharm

Trial Exhibit 7, col. 5, l. 64-68. If pioglitazone is similar to methyl substituents at positions 3 and 4, it stands to reason that it is "similar" to a methyl substituent at the 6-position as well.

Pioglitazone has Properties Similar to the Lead Prior Art Compound

15. Compounds that share similar structure often share similar properties. And given the structural similarities between the closest prior art compound and pioglitazone, the skilled artisan would not be surprised that the two compounds share similar properties.

16. Pioglitazone shares many properties with the prior art 6 methyl. Pioglitazone "exhibit[s] in mammals blood sugar-and lipid-lowering activity, and [is] of value as a therapeutic agent for treatment of diabetes and hyperlipidemia." Alphapharm Trial Exhibit 7, Preamble. The '777 also asserts that the claimed ethylated thiazolidine derivatives, including pioglitazone, "can be practically used as antidiabetic agents . . . ." Alphapharm Trial Exhibit 7, col. 1, line 36.

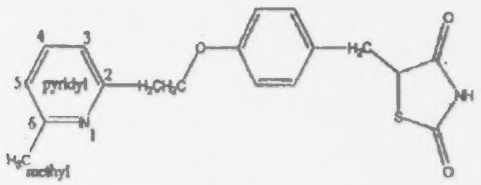
17. Similarly, according to the '200 patent, the prior art 6-methyl was "useful as, for example, remedies for diabetes, hyperlipemia and so on . . . ." Alphapharm Trial Exhibit 1, Abstract. In fact, Takeda claimed this compound, along with others, possessed "hypolipidemic [i.e, lipid-lowering] and hypolglycemic [sic, i.e., blood-glucose lowering] activities with low toxicity." Alphapharm Trial Exhibit 1, col. 1, lines 4-6. Moreover, when the inventors of the '200 patent were faced with a rejection by the Patent Office indicating that all of the compounds were obvious in light of an earlier patent disclosing thiazolidine compounds, the inventors' attorney responded that "the claimed compounds are superior to the known compounds of the cited [Diamond] reference in various pharmaceutical activities, such as hypolipidemic activity, pypoglycemic [sic] activity, etc." Alphapharm Trial Exhibit 2 at Alpha 70 to 71. As part of the response to the rejection, Takeda inventor Takeshi Fujita signed a declaration comparing the blood glucose and lipid-lowering effects of 9 of the compounds taught in the '200 patent,

including the 6 methyl, against those of the Diamond reference. Alphapharm Trial Exhibit 2 at Alpha 75 & 77.

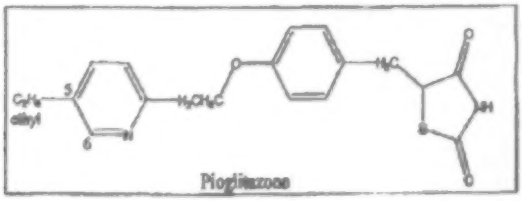
18. The Fujita declaration in the prosecution history of the '200 patent is significant for another reason. It provides motivation to one of skill in the art to pursue further examination of the 6 methyl. As noted above, the prosecution history of the '200 patent—which itself is publicly available and would be considered by one of skill in the art—compares the blood glucose and lipid-lowering properties of 9 of '200 patent compounds. One of those compounds was the 6 methyl. As the skilled artisan would readily appreciate upon review of this comparison, the six methyl was statistically superior to 6 of the 9 compounds relied upon. The superior efficacy of the 6 methyl would motivate one of skill in the medicinal chemistry art to make antidiabetic compounds having a structure similar to this very efficacious chemical structure.

Given the Similarity in Structure and Properties, Ciglitazone is an Obvious Modification of the Prior Art Compound Alone

19. On September 1, 1981 the '200 patent made three facts known to those of ordinary skill in the art of medicinal chemistry. First, a new compound existed with this formula:



Second, this new compound was useful as a remedy for diabetes. Third, of the numerous compounds disclosed, *the 6 methyl had the highest level of efficacy*. Based solely on these facts—made publicly available by the '200 patent and its prosecution history—one of ordinary skill in the art would have been motivated to search for new diabetic drugs and in that search would have been motivated to make compounds having similar structure and properties as the prior art 6 methyl, including this compound:



Pioglitazone

Simply put, given *only* the disclosure of the '200 patent and its prosecution history, pioglitazone is an obvious modification of the prior art 6 methyl.

The Prior Art Sohda Article Provides Additional Motivation to Make Pioglitazone

19. A year after the issuance of the '200 patent, Takeda published the results of its study of 101 thiazolidine compounds using the same testing parameters set forth in the Fujita declaration of the '200 patent: blood glucose- and lipid-lowering effects. Alphapharm Trial Exhibit 3 (I will term this prior art reference, the "Sohda Article" from here on). The authors measured potency, for each of the two effects, on a scale of 0-4, with 4 being the most potent, and presumably the most-promising, as a potential antidiabetic pharmaceutical compound.

20. The 6 methyl is listed as compound 58 in Alphapharm Trial Exhibit 3 on page 3586. It ranked a "3" in blood glucose-lowering and a "4" in lipid-lowering. Of the 101 compounds considered, only 6 other compounds scored as well. That the 6-methyl ranked in the top ~5% of the group in terms of desired effect is strong motivation to select it as a compound to

further study. Those of ordinary skill in the art of medicinal chemistry are today—just as they would be then—motivated to pursue new, more potent, drugs based on known drugs with favorable characteristics. Indeed, this was precisely the motivation for the Sohda article itself. The authors explain: "Since compound 1 (AL-321) [the known drug] was first found to possess potent hypoglycemic and hypolipidemic activities, various compounds having modified phenethyl moieties . . . have been synthesized." Alphapharm Trial Exhibit 3 at 3588. Standing alone, the high activity of the 6 methyl provides as strong motivation to select compound 58 as a "lead" compound for further testing.

21. In addition to the high score for desired effect, the Sohda article provides still further motivation to make incremental changes to the 6 methyl. The authors note that the 6 methyl compound "caused considerable increases in body weight and brown fat weight." Alphapharm Trial Exhibit 3 on page 3589. Perceiving this as a problem with a known potent compound would motivate one of skill in the art to make changes. The authors of the Sohda article themselves were motivated to attempt small structural changes to a known potent compound because it had slightly undesirable characteristics. The authors note:

> Among the compounds listed in Tables I and II, compounds 10, 12, 15, 18 and 25 showed more potent activities than 1, but these compounds caused considerable increases in relative liver weight and liver lipid at high dose levels or on chronic administration. As this undesirable effect may have been a consequence of the existence of two benzene rings in the molecule, we replaced one of them with other moieties.

Alphapharm Trial Exhibit 3 at 3588. The skilled artisan would be similarly motivated to attempt further substituent replacement to maintain the very desirable potency of the 6 methyl, while reducing the unwanted side effects of increased body weight and brown fat weight.

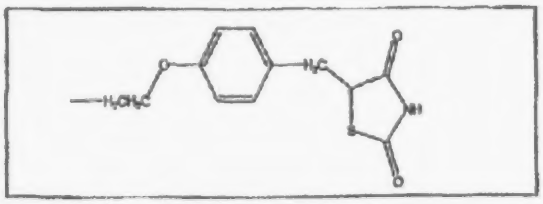
22. Furthermore, persons of skill in the art would have noted in their review of the Sohda article that the compounds containing pyridyl rings on the 'left hand side' of the structure (compounds 50-60) display high potency. It would have been further noted that of these compounds, the 6 methyl compound (compound 58)—the *only* example in this series with a substituent on the pyridyl ring—was the most potent. One of ordinary skill in the art—realizing that the 6 methyl substituent was responsible for increasing potency in the series—would thus have been *strongly* motivated to attempt further substituent replacement to maintain the very desirable potency of the 6 methyl, while reducing the unwanted side effects.

23. Moreover, the unwanted side effects observed for the 6 methyl compound would in no way have suggested that it was not worth tweaking. In fact, less than two years after the Sohda article appeared—and more than a year *before* the inventors filed the application for the '777 patent—the person of ordinary skill in the art would have learned that Takeda had *specifically claimed* the 6 methyl compound in claim 4 of the '779 patent. Alphapharm Trial Exhibit 5, col. 20, ll. 43-45 (claim 4). Thus Takeda itself published to the world in the '779 patent that substituted pyridyl rings, such as the 6 methyl, were novel and useful in the treatment of diabetes. Furthermore, in the prosecution history of the '779 patent, Takeda admitted that the 6 methyl had been claimed because this compound had become "important." Alphapharm Trial Exhibit 6, at Alpha 54.

24. But even if Takeda had not published that it was zeroing in on substituted pyridyl rings, the whole point of drug design is to maximize potency while minimizing toxicity following the most straightforward possible path. A person of ordinary skill in medicinal chemistry would have considered increases in brown fat and weight gain in test rodent to be at

worst unwanted, potential side effects, and would have proceeded to minimize them accordingly while preserving potency in the 6 methyl.

25. The motivation to minimize these side effects through systematic incremental changes to the 6 methyl is even stronger when the undesirable increases in body weight and brown fat weight are coupled with the authors' disclosure that "the partial structure (shown below)



is the essential structural feature for both glucose- and triglyceride-lowering activities." Given this, the person having ordinary skill would even more readily understand that discreet, and simple, modifications to the "pyridyl" ring of the 6 methyl—the moiety *not* responsible for the desired glucose- and triglyceride-lowering properties—would be expected to, successfully, affec the body weight and brown fat weight increases.

26. Finally, the Sohda article revealed the increased efficacy of the pyridine compounds when adding a methyl substituent to the unsubstituted pyridyl, compound 57 in the article. Triglyceride lowering activity increased by at least 40% as a result of the addition of a methyl group. The increase in efficacy was a consequence of the specific physicochemical effects on the molecule (e.g. increased lipophilicity) which occur when adding a CH_2 group. As Adding another CH_2 would further increase these effects on the compound and in following the trend of homologation, potentially increase activity. The Sohda article demonstrated a clear

trend and provided the motivation to perform routine homologation on pyridine rings with an expectation of improving the compounds profile.

27. While the '200 patent and file history discloses the 6 methyl compound, its usefulness, and its superior efficacy—which is enough by itself to render pioglitazone obvious to one of ordinary skill—the subsequent Sohda article is the key piece of prior art that the skilled artisan would look to. It not only discloses all of the facts disclosed by the '200 patent and file history but also provides further, multiple, explicit motivation to use the 6 methyl to obtain pioglitazone. Thus, although either the '200 patent and file history or the Sohda article—standing alone—render pioglitazone obvious, the Sohda article is particularly significant in this respect.

Routine Homologation Would Lead the Skilled Artisan from the Prior Art 6 methyl to Pioglitazone with a Reasonable Expectation of Success

28. In addition to these disclosures, however, it is important to consider the common knowledge in the medicinal chemistry art at the time of the invention. Specifically, it was known to focus on a "lead compound" and "tweak" it to result in a more effective and less toxic drug. A "lead" compound is a compound that has the desired activity but has some deficits, including unwanted side effects or toxicity. Development of the lead, then, is to maintain or improve the desired activity while reducing or eliminating the undesired activity, such as the authors' concerns about increases in brown fat or weight gain.

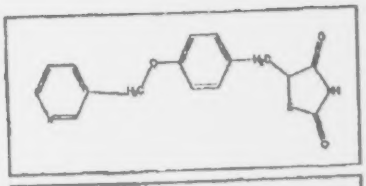
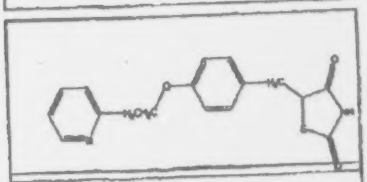
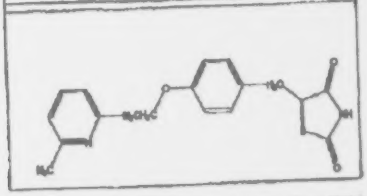
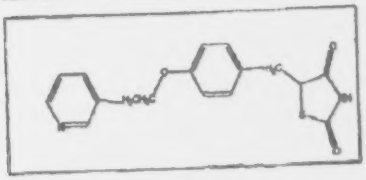
29. One of ordinary skill in the art of medicinal chemistry reviewing the prior art—either the '200 patent or the Sohda article—would have been motivated to select the 6 methyl as the "lead" compound for further testing. One skilled in the art of medicinal chemistry would have been motivated to "tweak" the 6 methyl to maximize its effectiveness by altering the position of the methyl on the pyridyl ring ("walking the methyl around the ring") and by

substituting an ethyl (C_2H_5) for the methyl in the available positions on the pyridyl ring. This latter process is called homologation, and is a routine procedure in lead optimization. Homologation, the stepwise lengthening of a substituent by addition of methylene units (CH_2), is based on the well-observed observation that such conservative modifications (such as an ethyl substituent replacing an methyl substituent) often result in improved potency or diminished toxicity. The nearest "relative" in the organic chemistry family to a methyl (CH_3) is an ethyl (C_2H_5). Though there is no absolute predictability in the field of medicinal chemistry, any person of ordinary skill in the art would have had a reasonable expectation of success in "tweaking" the lead compound in this way.

30. The skilled medicinal chemist would not proceed randomly, but would base his attempts on the available knowledge of prior research techniques and literature used in his field. Given the disclosures of the Sohda article, such a person would have recognized that the most straightforward course would have been conservative modifications to follow-up the observed potency-enhancing 6 methyl substituent: 1) examination of methyl substituents at the unexplored 3, 4 and 5 positions and 2) examination of the ethyl homologs at the same positions and comparison of the results of each substituent in test subjects.

31. Thus, the first step that any ordinarily skilled medicinal chemist would take in "tweaking" the 6 methyl would be to vary the position of the methyl (CH_3) substituent, in essence to "walk" the favorable substituent around the pyridyl ring. Such a step is taken with the expectation that the methyl substituent is causing the potent activity, but the position of the methyl on the ring (at the 6 position) may be causing the unfavorable side effects. That the methyl substitution increases potency follows directly from the published data in the Sohda article. There, the person of ordinary skill would observe the following values:

SA113

Compound	Structure	Total Potency
56		6 (3 and 3)
57		5 (3 and 2)
58		7 (3 and 4)
59		5 (3 and 2)

All, according to the article, "showed potent activities [but] they, especially 57 and 58, caused considerable increases in brown fat and weight gain." Alphapharm Trial Exhibit 3, at p. 3589. One of skill in the art would deduce from these data that the methyl substituent was responsible for the potent activity, particularly in that none of the others showed comparable values. Varying its position would be the first—but not the only—option to minimize these unwanted effects. Persons of ordinary skill in the art would synthesize and test methyl substituents at the 3, 4, and 5 positions on the pyridyl ring and compare their efficacy and toxicity results to that found

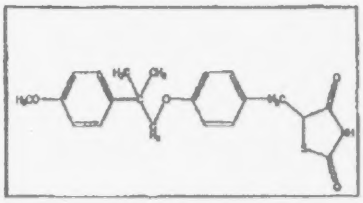
with the 6 methyl. A fair and accurate portrayal of the resulting structures can be found at Alphapharm Exhibit 281 [Exhibit N, attached].

32. The second route—which would probably but not necessarily be taken simultaneously—would be to synthesize and test homologs of the methyl-substituted pyridyls by switching to ethyl substituents at the same positions. Such small structural changes often have significant effects on potency or side effects due to subtle, predictable changes in the solubility and size of the molecule. The ability of such homologation to yield improvements in the activity profile in a series of compounds was well known at the time of the Sohda II article.

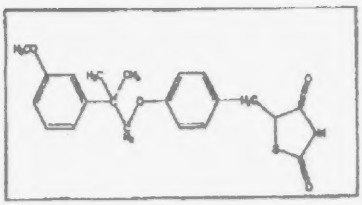
33. These are the only steps required to reach the alleged "invention" of pioglitazone, and encompass a total of only seven synthesized and tested compounds, in addition to the lead 6 methyl compound: the 5 methyl vs. the 5 ethyl (pioglitazone), the 4 methyl vs. the 4 ethyl, the 3 methyl vs. the 3 ethyl, and the 6 ethyl. Success was not dependent upon random variations of numerous parameters. Rather, the prior art instructed one skilled in the art to perform these steps in this particular order to arrive at pioglitazone. These choices are hardly surprising; they are in fact expected, and anyone of skill in the art would have made them. Furthermore, there are no intermediate compounds involved in the synthesis of pioglitazone which could potentially teach away from the desired compound.

34. Walking the favorable substituent around the ring to examine positional effects was known well before Takeda filed the application which issued as the '777 patent. Indeed, the '200 adopts the concept. There, Takeda examined the effect of "walking" a methoxy (CH_3O) substituent around a phenyl ring, respectively occupying the 4, 3 and 2 positions on the described phenyl ring. Alphapharm Trial Exhibit 1 ('200 Patent), example compounds 31, 32, & 33. Examples 18 and 19 also demonstrate the same concept with methoxy (CH_3O) substituents at

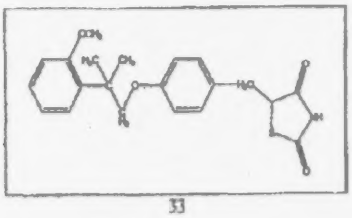
positions 2 and 4 on the phenyl ring. These examples are set forth completely and accurately below for ease of reference:



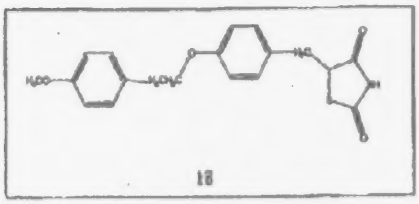
31



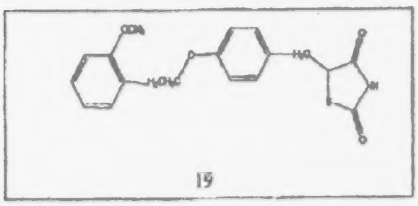
32



33



18



19

The effect of a chloro (Cl) substituent at different positions on a phenyl ring was examined in compounds 1 and 2.

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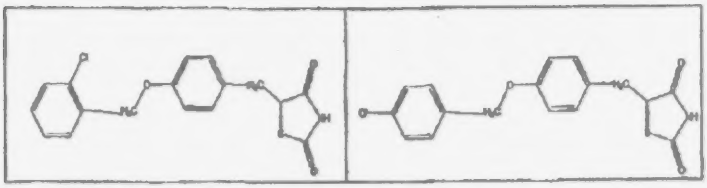
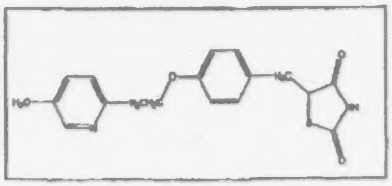
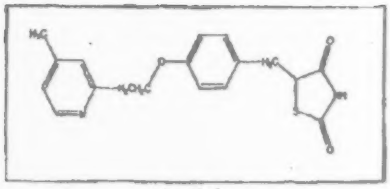


1 2

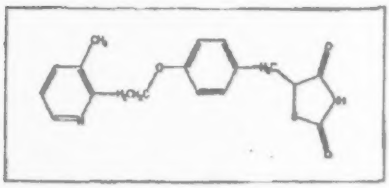
35. Internally at Takeda, once the high efficacy of the 6 methyl was known, synthesizing and testing methyls at alternate positions had a high priority, as it would have to others of ordinary skill in the art. This point is illustrated by Takeda's own internal documents that demonstrate the evaluation of methyl at various positions on the pyridyl ring. Alphapharm Trial Exhibit 11 (TAK 00117925). Takeda researchers, armed with the same knowledge available to the public regarding the efficacy of the 6 methyl, took the next logical step and "walked" the methyl substituent around various positions on the pyridyl ring and subsequently tested these compounds to see if this slight structural modification improved the overall profile as compared to the 6 methyl. Takeda's own synthesis efforts as reported in that 1984 Takeda document are set forth completely and accurately below:



5 methyl



4 methyl

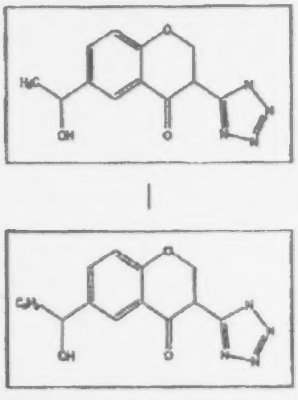


3 methyl

36. The '200 and the '779 patents each speak in terms of "alkyl" substituents and components, alkyls being linear chains of carbon atoms singly bonded to other carbon atoms or hydrogen atoms. Alphapharm Trial Exhibit 1 ('200 patent at claim 1) and 5 ('779 patent at claim 1). In medicinal chemistry, the most common examples of alkyls are methyl (CH_3) and ethyl (C_2H_5). Takeda took the same position, referring in the '200 and '779 patent specification to the substituents on ring systems, "examples of such substituents may be mentioned lower alkyls (e.g., methyl, ethyl, etc.)." Alphapharm Trial Exhibit 1, '200 patent, col. 2, l. 45 & Alphapharm Trial Exhibit 5, '779 patent, col. 2, l. 45. Takeda's choice of language suggests that among the alkyls methyl and ethyl substituents may be preferred. Indeed, in its prosecution of the '779 patent, the applicant specifically represented that the new class of substituents to be claimed in the '779 patent was a "relatively ***narrow*** and ***well-defined group*** of constituents" that "would function as a hypolipidemic and hypoglycemic agent as specified in the instant disclosure." Alphapharm Trial Exhibit 6, Alpha 60-61. It would hardly come as a surprise therefore that an

ethyl substituted pyridyl could be selected from the '779 patent claim 1 genus. Pioglitazone as claimed in the '777 patent is merely an obvious species of the '779 genus.

37. Further, Takeda itself recognized the standard use of homologation in drug development eight years before it applied for the '777 patent. In 1978, Takeda researchers published the results of studies on anti-anaphylactic agents. Alphapharm Trial Exhibit 12, (the "Nohara article," after its lead author). After identifying a lead compound with the ethyl substituent C_2H_5 at the 6 position on a phenyl ring, the researchers identified seven metabolites. Takeda synthesized and tested for biological activity several metabolites as well as analogs of two metabolites, 2 and 3. A total of 28 compounds were synthesized to reference against the lead compound. Metabolite 2 is of particular interest. That metabolite consisted of a methyl group attached to a carbon which linked a hydroxyl group to the phenyl ring. Below is a fair and accurate example of the metabolite disclosed in the Nohara article:



38. In addition to synthesizing and testing metabolite 2, Nohara et al. also examined homologous compounds including compound 14a (the ethyl homolog of compound 2). This methyl to ethyl homologation is exactly as practiced in the '777 patent and demonstrates that

such an approach was routine in the art at that time. In fact, Nohara et al did not even bother to explain why the methyl was replaced with an ethyl analog, since the decision to do so is routine in the industry and therefore did not require an explanation when peer reviewed.

39. Indeed, as noted above, many examples provided in the '200 patent demonstrate that Takeda was aware that substitution of a methyl with an ethyl should be carried out to test for useful compounds. Compound 3 in example 9 is the same compound as example 4, except that the methyl substituent CH_3 in compound 3 was replaced with the ethyl substituent, C_2H_5, in compound 4. Alphapharm Trial Exhibit 1 ('200 patent) at col. 8. Compounds 5 through 9 continue the homologous series and demonstrate considerable thoroughness in exploring the effect of chain length. Alphapharm Trial Exhibit 1 ('200 patent) at cols. 8-9. Takeda practiced the same methyl-ethyl substitution on an aromatic ring in compounds 15 and 16. Alphapharm Trial Exhibit 1 at col. 9. These are the exact replacements which led to the claimed invention in the '777 patent. In fact, compounds 15 and 16 of the '200 patent share the same structural relationship as c and I of the '777 patent, differing only in having a substituted phenyl ring rather than a substituted pyridyl ring.

Pioglitazone was the Natural Result of the Prior Art 6 methyl and Routine Homologation

40. In the context of drug design, the replacement of a methyl substituent at four locations on a pyridyl ring with the next natural replacement hardly constitutes extensive experimentation, especially when following up a promising lead such as the 6 methyl. Takeda itself had taught the necessity to make all related compounds, by publishing so many analog examples both in its patents and the literature. Once that obvious ethyl-substituted series of compounds were synthesized and tested on the pyridyl ring, anyone skilled in the art would have determined that the series had superior blood-glucose lowering and triglyceride lowering activity with "extremely low toxicity" as reported in the '777 patent specification.

The Results for Pioglitazone were Not Surprising

41. While prosecuting the '777 patent, the inventors attempted to show that the potency and toxicity results for pioglitazone were nevertheless surprising—and thus not obvious—relative to the structurally similar compounds with methyl substituents at the 6, 5, 4 and 3 positions on the pyridyl ring. Alphapharm Trial Exhibit 7, Table I, cols. 5-6. The prior art 6 methyl proved more potent than pioglitazone but the inventors instead asserted that pioglitazone had "extremely low toxicity" as compared with the 6 methyl. Alphapharm Trial Exhibit 7, '777 patent, col. 6, ll. 5-6. Based upon my experience, I do not believe that improvement of the potency or toxicity results of pioglitazone over the prior art were surprising in the context of medicinal chemistry.

42. In the '777 patent, the inventors disclosed on Table I that pioglitazone reduced blood glucose and triglycerides by a little over 3 times that found in the 3, 4, or 5 methyl compounds. That is hardly a substantial improvement whereby one would be surprised at the result, even for the very conservative change from methyl substituent to an ethyl substituent, as in pioglitazone, on the same basic compound. Persons of ordinary skill in the art would be motivated to make just such a conservative change precisely because they have a reasonable expectation of success of improving the lead compound in this way. A conservative change would be expected to maintain the very high potency of the 6 methyl, while "tweaking" it slightly to reduce its unwanted side effects, i.e., weight gain and brown fat increases.

43. Moreover, it is puzzling to me that Takeda chose not to bring to the examiner's attention the existence of the '779 patent. In that patent, Takeda had already claimed the novelty and utility of lower alkyls such as methyl and ethyl substituents on pyridyl rings. Alphapharm Trial Exhibit 5, col. 20, claims 1-6. Thus, Takeda can hardly allege surprise at the beneficial results of substituting an ethyl for methyl on the pyridyl as it claimed in the '777 patent. If the

examiner had had the '779 patent before him, he may have held Takeda to a standard for surprising results higher than a mere 3 fold increase between some of the methyl-substituted pyridyls and the ethyl-substituted pioglitazone.

45. I state under penalty of perjury that the above is true and correct to the best of my personal knowledge.

Executed on: November 18, 2005

Henry I. Mosberg

SA122

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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF NEW YORK

Takeda Chemical Industries, Ltd., and Takeda Pharmaceuticals North America, Inc., Plaintiffs, v. Ranbaxy Laboratories, Ltd., et al., Mylan Laboratories, Inc., et al., Watson Pharmaceuticals, Inc, et al., Alphapharm Pty, Ltd., et al., Defendants.	Civil Action No. 03 CV 8250 (DLC) 03 CV 8253 (DLC) 03 CV 8254 (DLC) 04 CV 1966 (DLC) (Consolidated for trial) Honorable Denise L. Cote

DECLARATION OF DOUGLAS R. MORTON, JR., PH.D.

SA123

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SA124

I. BACKGROUND

1. My name is Douglas Ross Morton, Jr., Ph.D.

2. I was born on August 5, 1945 in Chicago, Illinois. I currently reside at 5218 Grand Arbre Trail, Portage, MI 49024.

3. Currently, I am a member of the American Chemical Society, the American Diabetes Association, and the American Association for the Advancement of Science.

4. I received an A.B. (Chemistry Major, High Honors in Chemistry, magna cum laude) from Kenyon College, Gambier, Ohio in 1967.

5. I received my Ph.D. in Organic Chemistry from Columbia University, New York, NY (Research Advisor: Professor Nicholas J. Turro) in 1971.

6. I had a postdoctoral appointment in Organic Chemistry at Stanford University, Palo Alto, CA (Professor William S. Johnson - deceased) from 1971-1973.

7. I am the author of 45 peer-reviewed publications and a named inventor on 44 United States patents. Trial Exh. 102 is my curriculum vitae, which includes a complete list of my publications and patents.

8. I first joined The Upjohn Company as a Research Scientist in the Experimental Chemistry Research Department in Kalamazoo, MI in 1973. I worked in that capacity until 1981, during which time I invented and synthesized novel variants of naturally-occurring metabolites of arachidonic acid, a polyunsaturated fatty acid important to maintaining normal physiology, many with significant biological activity on blood platelets and on the gastrointestinal tract. I contributed to the structural elucidation of prostacyclin (PGI_2) and invented and synthesized novel, chemically stable analogs of this naturally-occurring substance for biological evaluation. I also selected compounds that were profiled for potential evaluation in humans for the treatment of platelet disorders.

9. From 1981 to 1984, I was the Research Head of Experimental Science I, at The Upjohn Company, in Kalamazoo, MI. In this position, I led a group of synthetic chemists in the discovery of novel variants of naturally-occurring metabolites of arachidonic acid. Through this position I assumed increasing responsibility for leadership of gastrointestinal ("GI") projects based on prostaglandin antisecretory and cytoprotection properties. I also led the initial drug development project team for arbaprostil (ARBACET), a gastric antisecretory and cytoprotective prostaglandin compound.

10. In 1984, and continuing through 1985, I assumed the position of Associate Director of Diabetes and Gastrointestinal Diseases Research, also at The Upjohn Company in Kalamazoo, MI. It was at this time that I assumed a leadership role for GI (chemistry and biology) and type 2 diabetes mellitus ("Type 2 Diabetes") (chemistry) drug discovery programs. I also ran the H^+-K^+ ATPase inhibitor drug discovery project, which led to a potential clinical candidate (PNU-69167; disaprazzole).

11. From 1985 to 1987, I was the Director of Diabetes and Gastrointestinal Diseases Research at The Upjohn Company. In this capacity, I assumed responsibility for drug discovery and development programs in GI and Diabetes. My research group prepared and evaluated compounds for the purpose of helping to decide whether they should be entered into The Upjohn Company's pharmaceutical development program. The compounds my group evaluated included pioglitazone (for the treatment of Type 2 Diabetes) and disaprazole (a depo-delivered H^+-K^+ ATPase inhibitor for peptic ulcer healing). I had the responsibility for managing collaborative interactions with various third-party firms for in- and out-licensed GI and Diabetes development candidates. These third-party firms included Chugai, Takeda, and Ono Pharmaceuticals.

12. I was the Director of Metabolic Diseases Research, at Upjohn from 1987 through 1990. In this position I assumed responsibility for Upjohn's drug discovery and development programs in Metabolic Diseases (diabetes and atherosclerosis). My research group prepared and/or evaluated compounds as development candidates for NIDDM (β-guanidinopropionic acid) and for atherosclerosis (fine particle COLESTID).

13. During the period from 1990 through 1991 I served as the Director of Medicinal Chemistry Research, at Upjohn.

14. In 1994 I was appointed as Vice President of Discovery Research, at Upjohn. My responsibilities expanded beyond Medicinal Chemistry to include all Discovery Chemistry functions (Computer-Assisted Drug Design, Protein Biochemistry, and Physical and Analytical Chemistry).

15. From 1995 through 2003 I served The Upjohn Company and its merged and successor entities, including: Pharmacia & Upjohn, Inc., Kalamazoo, MI; Pharmacia & Upjohn, Inc., Peapack, NJ; Pharmacia Corp., Peapack, NJ; and Pfizer, Inc., Peapack, NJ, in the following positions: Vice President of Discovery Research; Group Vice President of Technology Acquisitions and Operations, and Vice President of Worldwide Discovery and Strategic Alliances.

16. From November 2003 through the present I have been the Chief Executive Officer of the Southwest Michigan Innovation Center, located in Kalamazoo, MI. In this capacity, I am responsible for assisting the scientific advancement of tenant/client companies, insuring the Center's operational intactness, nurturing connections between the Center and the external community, and monitoring and evaluating bioscience trends on the regional, national and international levels.

17. From 2003-2004, I was a member of the Scientific Advisory Board of Celltech R&D Ltd., Slough, Berkshire, England. I was a member of the Board of Directors of TissueInformatics, Inc., Pittsburgh, PA, from 2003 until the company was acquired by Paradigm Genetics in March of 2004. I have been a member of the Industrial Advisory Board of Cleveland Clinic Foundation Innovations, Cleveland, Ohio since 2004. I am a member of the following Boards of Directors: Icoria, Inc. (formerly Paradigm Genetics, Inc.), Research Triangle Park, NC; Core Technology Alliance Corporation, Ann Arbor, MI; and MichBIO, Lansing, MI. I am presently also serving as interim CEO of Icoria, Inc., Research Triangle Park, NC.

18. I am in no way being compensated for my testimony, although I am receiving reimbursement for my travel and legal expenses in connection with my testimony in this case. I have no interest in the outcome of this litigation.

II. THE TAKEDA/UPJOHN COLLABORATION

19. When I assumed the Associate Directorship of the Diabetes and Gastrointestinal Research Unit at The Upjohn Company in 1984 I became involved in the Takeda/Upjohn collaboration in researching thiazolidinediones. While that was the beginning of my involvement, that collaboration had already been ongoing for some years. By 1984, Upjohn and Takeda had already investigated ciglitazone [Takeda internal no. ADD-3878, Upjohn internal no. U-63,287] among many other thiazolidinediones. Ciglitazone, the first thiazolidinedione that was regarded as a pharmaceutically viable option, was synthesized by Takeda in the late 1970s. Through the early 1980s, Takeda and Upjohn collaborated in the development and testing of ciglitazone. In fact, ciglitazone had made it through the initial stages of human clinical trials until such work was discontinued,

primarily because long-term administration was found to cause cataract formation in rats.

20. By 1983, ciglitazone had been dropped and numerous other thiazolidinediones had been tested. The data on these compounds showed that thiazolidinediones generally were capable of lowering blood glucose and plasma triglycerides in animals presenting symptoms of Type 2 Diabetes, and of lowering triglycerides in normal animals, but exhibited significant toxicities when administered in therapeutically effective doses. From these findings it was concluded that thiazolidinediones seemed somehow able to ameliorate "insulin resistance" (i.e., a condition in which the body no longer responds (in varying degrees) to insulin's message to metabolize glucose), and so were sometimes described as "insulin sensitizers."

21. Notably, Upjohn and Takeda's investment of time, resources and capital into this research went against the grain of then-current industry thinking. I recall that Upjohn faced frequent challenges on its approach from other leaders in the diabetes field for pursuing thiazolidinediones for the treatment of Type 2 Diabetes, instead of the then-industry standards - insulin secretagogues (i.e., compounds which attempted to combat insulin resistance by causing the pancreas to create more insulin) and treatment of late-stage sequelae (late-stage consequences of Type 2 Diabetes, such as neuropathy, nephropathy, and retinopathy). Throughout the mid 1980s, scientists from other major pharmaceutical companies made it known that they believed research into insulin sensitizers to be in an unestablished, unproven, and risky direction. Our understanding, at the time, was that diabetes researchers and management at these companies thought insulin sensitizers to be a form of radical and unfounded thinking in diabetes treatment.

The Takeda/Upjohn partnership was a pioneering collaboration in a new direction of diabetes treatment involving insulin sensitization. As a result, however, we were also working in largely uncharted terrain.

22. An example of the evolution in our knowledge and thinking can be found in an article entitled, Sohda T. et al., "Studies on Antidiabetic Agents II. Synthesis of 5-[4-(1-Methylcyclohexylmethoxy)-benzyl]thiazolidine-2,4-dione (ADD-3878) and Its Derivatives," Chem. Pharm. Bull. 30:3580-3600 (1982)) ("Sohda II") [Trial Exh. 076]. This reference teaches that Compounds 57, the unsubstituted 2-pyridyl {5-[4-[2-(2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione} and 58, the 6-methyl substituted 2-pyridyl {5-[4-[2-(6-methyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione} "caused considerable increases in body weight and brown fat weight." Id. at 3589 At the time, it was known that brown fat had to do with thermogenesis in rodents but we were not sure of a direct correlation with physiology in humans. We also knew that brown fat could have something to do with sugar metabolism, but were, again, unsure of any relationship to human physiology. These were then matters of scientific debate. We did, however, know that the pathology of Type 2 Diabetes, referred to at the time as Non-Insulin Dependent Diabetes Mellitus ("NIDDM"), suggested that obesity contributed to insulin resistance. We also knew that, generally speaking, obesity and any increase in obesity in a patient suffering from NIDDM was thought to be a clear adverse health effect. Therefore, because of data indicating that pyridyl derivatives caused such adverse health effects, people involved in or interested in this research, reading Sohda II at the time, myself included, would conclude that this reference taught away from the pyridyl compounds.

23. As research continued, however, we came to the conclusion that increases in body weight and brown fat weight were sometimes a corollary to effectiveness in thiazolidinediones, and that brown fat was not a significant factor in humans. However, based on the wealth of data available to us, it seemed clear that this class of compounds was characterized by common toxicities to the eye (cataracts), heart, liver and red blood cells (anemia). See Trial Exh. 081 (A-15-13, p. 17, TAK-00383425, 442). From the point of view of toxicity, these effects became more important than brown fat or body weight gain.

24. In developing a successor to ciglitazone, our primary focus was on finding a compound that did not exhibit these toxicities, and which was five to ten times more potent than ciglitazone.

25. Of particular concern to our team was cataractogenesis. Cataract formation was an important toxicology parameter in the United States Food and Drug Administration (FDA). Based on this understanding and the fact that it was found to occur with ciglitazone, both Takeda and Upjohn placed a strong emphasis on the test used to indicate cataractogenesis, which was known as the chick lens assay. See Trial Exh. 107 (Upjohn Letter Regarding Utility and Importance of in vitro Chick Lens Assay, TAK-00384319-20); Trial Exh. 108 (Letter from Upjohn to Takeda Discussing Chick Lens Screen, TAK-00384321); Trial Exh. 082 (Minutes of March 13, 1984 Strategic Meeting, TAK-00366984-86). A failure in the in vitro chick lens assay would cause a compound to be ruled out for development.

26. Similarly, cardiomegaly (increase in heart weight) was of paramount concern. Were a compound to exhibit statistically significant heart enlargement, it too would be precluded from further consideration.

27. Thus, by 1984 Takeda and Upjohn had a wealth of data resulting from years of research, but lacked a promising successor compound which exhibited sufficient pharmacological activity without the toxicity that ended ciglitazone's development. Because of this extensive work, Takeda and Upjohn researchers were among the most skilled in the field. This group of scientific investigators had certainly reviewed, if not authored, likely all of the publicly available information regarding thiazolidinediones. Despite this wealth of information and expertise, however, researchers involved in the Takeda/Upjohn collaborstion were without a clear path by which to develop a thiazolidinedione compound that would be both effective and safe.

28. During the early-to-mid 1980s, there was no way that anyone could reliably predict the degree of efficacy or toxicity of various structural thiazolidinedione derivatives. They had to undergo time and resource-intensive testing in animals. Even a seemingly simple change in chemical structure can have a profound impact on the biological activity of a molecule, because a relatively minor structural change may change various aspects of the molecule including its shape or overall conformation, electron density, and/or its physical properties (e.g., solubility), all of which affect the way in which a molecule may interact with its protein target(s) (sometimes referred to as receptors). This was further complicated by the fact that, at the time, the particular receptor at issue (and so its relevant binding pocket) were unknown. One simply could not predict the impact of such a change on the protein-binding that the molecule is interacting with that might be responsible for its biological effects.

29. As a result, Takeda and Upjohn used a "shotgun" approach to thiazolidinedione development, yielding data on a vast number of compounds. That data was then analyzed

to see if we could discern a relationship between chemical structure and biological properties. Some comparisons were relevant and some were not. Of the compounds not blacked out in Table 1 of the A-15-34 report (described later) (Trial Exh. 083), I would consider a comparison of pioglitazone to ciglitazone to be the starting point, given the amount known about the latter compound. I would then want to compare pioglitazone to the other alkyl substituted pyridines. I would not consider a comparison between pioglitazone, a 5-ethyl pyridyl [alkyl-substituted] compound, and ADD-3894, an unsubstituted compound, to be as immediately critical as the comparisons to alkyl-substituted pyridines because the structural and electronic properties of an alkyl-substituted pyridine ring differ from those properties in an unsubstituted-pyridyl compound.

30. Given all these considerations, Upjohn and Takeda used this "shotgun" approach to development in searching for a post-ciglitazone compound, both to increase efficacy and to get away from its toxicity. This approach was discussed at and memorialized in the Minutes of Takeda-Upjohn Meeting on Collaboration in Antidiabetic Drug Discovery, dated March 13, 1984. Trial Exh. 082 (TAK-003669S4-86). I was at that meeting and have an independent recollection of it. To the best of my recollection, these minutes accurately reflect the happenings of that meeting.

31. As memorialized in the meeting minutes, Takeda was to "select about 50 antidiabetic leads on the basis of hypoglycemic activity in the KKAy mouse and the Wistar-fatty rat. Aside from potency, the selection criteria should also include uniqueness in chemical structure." Id. (TAK-003669S4-86). Such "uniqueness in chemical structure," was part of our plan for finding a safe alternative to ciglitazone. We were concerned that toxicity

problems might be general to thiazolidinediones and/or to particular sub-structures within some of the molecules. Thus, "structural uniqueness" adds information from a structure activity point of view, and lessens the likelihood of finding that compounds with similar structure exhibit similar toxicities. Another structural consideration revolves around the scalability of a compound, concerning whether the compound could be synthesized on a commercial scale. Of note, I cannot recall any mention or concern of patentability at any meeting between Takeda and Upjohn during the period from March of 1984 through January of 1986. The mission of our collaboration was focused on identifying a compound that was efficacious and of extremely low toxicity.

32. Generally, of course, patentability is eventually a consideration for all research-based drug companies, because that exclusivity is the only way that they can recuperate the enormous investment needed to discover and develop new drugs. But in our thiazolidinedione research and selection process patentability was not a driving consideration.

33. In the agreements reached at the meeting of March 13, 1984, responsibilities were divided between and among Upjohn and Takeda and a timetable set. As the minutes reflect, the fifty compounds originally identified were to be narrowed to about ten, then five, then one. We agreed to a further meeting in August of 1984 to jointly review our research and to select nine to ten leads, to be further narrowed to four to five leads. Unfortunately, the work proved difficult, and some delays set back the schedule by roughly three months, so the meeting set for August 1984 took place at the end of October, 1984.

34. Before the October 1984 meeting, Upjohn carried out its own testing of many if not all of the 50-odd compounds selected for investigation by Takeda. Some of the compounds selected for evaluation had already undergone analysis in the Upjohn laboratories prior to March of 1984, such as ADD-3878 (ciglitazone) and ADD-3959. See Trial Exh. 106 (TAK-00384340-41); Trial Exh. 107 (TAK-00384319-20); Trial Exh. 108 (TAK-00384321). I cannot now recall the particulars of the many compounds that we analyzed, but I clearly recall that we independently assayed some if not all of the fifty "leads" selected by Takeda.

35. I know that Upjohn carried out various efficacy and toxicity experiments on these "lead" thiazolidinedione compounds, including the in vitro chick lens assay and four-day efficacy screens in KKA^y (diabetic) mice.

36. In the early 1980s (I cannot recall a specific date) Takeda had provided Upjohn with a breeding colony of KKA^y mice specifically for use in testing potential antidiabetic compounds for efficacy. See Chang AY et al., "The Upjohn Colony of KKA^y Mice: A Model for Obese Type II Diabetes," in Diabetes, at 466-470 (1985) (Trial Exh. 110). During the collaboration, these animals were used in the screening and evaluation of thiazolidinedione chemotypes related to the collaboration.

37. Although I do not recall the exact KKA^y experimental protocol used at Upjohn, I have seen the A-15-34 report which was discussed at the October 1984 meeting, and Upjohn's test protocol was substantially similar, if not identical to, the protocol described in that document. Trial Exh. 083 at TAK-00400122 (A-15-34).

38. I was of the belief in the early-to-mid 1980s and am today that the KKA^y mouse represents the best disease model to identify and develop antidiabetic compounds relative

to humans. The blood profiles of KKA^{y} mice are very similar to humans and therefore provide a very accurate in vivo model of Type 2 Diabetes in humans.

39. KKA^{y} mice are, however, very sensitive animals. Changes in light, noise and temperature in addition to other external stimuli can affect mating, reproduction, litter sizes and mortality, and pharmacological responses. Investigators using this model had to keep these sensitivities in mind when evaluating data from this model. Investigators had to determine whether a given experimental result was due to a pharmacological response. Importantly, investigators must have a feel for the compounds' respective properties to know whether an experiment was meaningful or flawed. In consideration of an investigator's knowledge and evaluation it was acceptable, and in many cases necessary, to disregard an experiment which, based on this knowledge and experience, was flawed and therefore produced unreliable data.

III. DECISION TO DEVELOP PIOGLITAZONE (AD-4833)

40. In late October, 1984, I traveled to Osaka, Japan with Drs. Dulin and Lund of The Upjohn Company to meet with senior Takeda scientists and management to select a new compound for codevelopment.

41. At this meeting a Takeda scientist (whom I cannot remember) presented a summary report containing Tables 1 and 2 found in the A-15-34 report (Trial Exh. 081). Although I do not recall reviewing the A-15-34 report in its entirety, I do have an independent recollection of Tables 1 and 2 and the data contained therein. The data on these tables formed the basis for our joint decision to focus on five particular compounds (marked in handwritten circles on Table 2) and to pursue development of pioglitazone. We relied on this summary data as the basis for our decision to develop pioglitazone. These summary

reports were the fruit of many months of labor and consisted of the synthesis of thousands of pages of data, data from both sides of the Pacific.

42. Upjohn did not have a policy of attempting to recreate or verify each and every one of Takeda's experimental results as communicated in these types of documents. Upjohn received data regarding hundreds of compounds. Verifying each and every endpoint for each and every compound would have been an imprudent use of our combined, yet limited resources. Notably, however, Upjohn did not rely solely on Takeda's efficacy and toxicity data when making its development decisions. Although there was a free exchange of data, in its own business interest Upjohn performed its own independent analyses on compounds that appeared interesting for further study (including many of the A-15-34 compounds). Through this testing, Upjohn, without exception, confirmed the data that Takeda summarized in its reports that were forwarded to Upjohn. Furthermore, the relationship with Takeda was such that Upjohn could have access to any compound it chose for confirmatory testing. Trial Exh. 103 (Takeda/Upjohn Co-development Agreement, TAK 00097692-95). In the history of my involvement with the pioglitazone project, there was never any disagreement between data reported to Upjohn by Takeda and the data that Upjohn independently generated (within typical variation inherent in animal experimentation) or the conclusions drawn from that data.

43. AD-4833 (pioglitazone) was a joint selection at the October 30, 1984 meeting. There was some discussion between Upjohn and Takeda on the issue of potency versus safety (therapeutic ratio). Trial Exh. 084 (Takeda Notes, TAK-00366387-92)[1]; Trial Exh. 086

[1] I have an independent recollection of a discussion of this subject matter at the October 30, 1984 meeting in Osaka. Although I do not recall seeing these notes at the time, this document accurately reflects Takeda's initial presentation of data at our meeting on October 30, 1984.

(Minutes of Upjohn/Takeda Meeting of October 30, 1984, TAK-00384248-50)[2]. The key parameter to Upjohn was the therapeutic ratio (safety ratio)[3] of a candidate compound - Upjohn selected pioglitazone on this basis. Takeda preferred some of the far more potent compounds, although they had greater toxicity and thus a narrower therapeutic index. In the end, the decision made by Upjohn and Takeda was collaborative and in total agreement: pioglitazone met our criteria of being five to ten times more potent than ciglitazone, it exhibited extremely low toxicity ("clean" at 100mg/kg/day and in the chick lens assay), and was superior in terms of its therapeutic index to all other compounds investigated. Pioglitazone was the only compound that was "clean" in all toxicity parameters of concern, namely, the in vitro chick lens assay, heart, liver, and erythrocytes.

44. We continued through 1984 to evaluate each of the five compounds selected at the October 1984 meeting. Based on interim data from longer-term (90 day) toxicological analysis of the five lead compounds, pioglitazone was the only compound that proved to be clean. On March 7, 1986, Takeda and Upjohn reached a final consensus that AD-4833 (pioglitazone) would be the candidate for development. See Trial Exh. 087 (Meeting Minutes of March 7, 1986, TAK-00384557-58).

IV. CONCLUSION

45. Over the course of my many dealings with Takeda, I found Takeda and its researchers to be solid scientists, and an extremely honest and ethical business partner. Upjohn and Takeda had a wonderful collaborative relationship, a relationship founded on mutual trust

[2] I have an independent recollection of reviewing these minutes and of the topics of discussion at the meeting. These minutes accurately reflect that subject matter.
[3] The wider the margin between the minimum efficacy and the minimum toxicity of a compound the greater the therapeutic ratio, or safety margin, of that compound.

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and confidence arising from the quality of the scientific work. Personally, I hold Takeda's scientists, particularly Drs. Meguro, Fujita, Sobda, Ikeda, and Iwatsuka in the highest regard. I have worked extensively with these scientists and have, on many occasions, reviewed Upjohn data that confirmed their methods, data, assessments, evaluations, and conclusions.

I declare under penalty of perjury that the foregoing is true and correct. Executed on November 16, 2005

Douglas Ross Morton, Ph.D.

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OFFICE OF THE CLERK
SUPREME COURT, U.S.

IN THE

Supreme Court of the United States

ALPHAPHARM PTY., LTD. and GENPHARM, INC.,

Petitioners,

v.

TAKEDA CHEMICAL INDUSTRIES, LTD. and TAKEDA PHARMACEUTICALS NORTH AMERICA, INC.,

Respondents.

ON PETITION FOR A WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

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CORPORATE DISCLOSURE STATEMENT

Petitioners' corporate disclosure statement was set forth at page *iv* of the Petition for a Writ of Certiorari. There are no amendments to that statement.

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REPLY ARGUMENT

I. The Evidence of Obviousness Could Not Be Fairly Evaluated as a Result of the "Teaching, Suggestion, or Motivation" Test

Takeda maintains that the Federal Circuit did nothing more than affirm the "all the evidence" approach recommended in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). But the Federal Circuit panel did anything but apply either § 103 or *Graham*. Neither the statute nor *Graham* requires the patent challenger to show specific motivation to select the closest prior art. That the Federal Circuit cited § 103, *Graham*, and *KSR International Co. v. Teleflex, Inc.*, 127 S. Ct. 1727 (2007) is of little warrant. What matters is how the lower courts applied these decisions. *See, e.g., Freedman Seating Co. v. Am. Seating Co.*, 420 F.3d 1350, 1363 (Fed. Cir. 2005) (reversing judgment of nonobviousness where *Graham* cited but differences over the prior art insufficient to warrant a patent grant); *Jones v. Hardy*, 727 F.2d 1524, 1529 (Fed. Cir. 1984) (noting "*Graham*, supra, was cited but its guidance was not applied").

A. Both Lower Courts Would Only Accept Obviousness if the Closest Prior Art Were the Best Candidate to Select

The Federal Circuit panel squeezed Alphapharm through a standard no patent challenger could meet: specific motivation that the closest prior art "would be the *best* candidate [to select] as the lead compound"

(A16)[1] and motivation to modify that best compound in exactly the manner claimed (A11). These are not factual inquiries under *Graham*, as Takeda asserts. (Opp. 10.) Instead, they are artificial legal hurdles. What led this Court to grant certiorari in *KSR* was dismissal of common sense in favor of "principal reliance on the TSM test." *KSR*, 127 S. Ct. at 1738. This Court confronts the same problem.

Takeda asserts that under *KSR* all patent challengers must prove both what starting point the skilled person would have selected ("lead compound"), *and* prove motivation to modify the compound in such a way as to reach the claimed invention. (Opp. 14.) Absent those proofs, so the argument goes, a challenger engages in impermissible hindsight. Takeda's interpretation of *Graham* and *KSR* is misplaced. This Court's *Graham* factors must look with a kind of hindsight—knowledge of the patent—to determine the scope of the prior art *and* determine any difference between the prior art and the claimed invention. *See* 35 U.S.C. § 103 (requiring factfinder to assess "the differences between the subject matter sought to be patented and the prior art"). That difference requires a determination of the closest prior art, and—starting there—whether the skilled person would arrive at the claimed invention. This differs from the improper hindsight of imparting to the skilled person the claimed subject matter and then hypothetically guiding her to a known end. *See, e.g., Monarch Knitting*

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[1] "A__" refers to the petition appendix to this Court. "SA__" refers to Alphapharm's Supplemental Appendix to this Court. "RA__" or "R-JA__" refer to the Unified Joint Appendix in Federal Circuit No. 06-1329.

Mach. Corp. v. Sulzer Morat GmbH, 139 F.3d 877, 881 (Fed. Cir. 1998) ("[d]efining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness").

B. Takeda Attempts to Mask the District Court's Errors of Law as Nonreviewable Issues of Fact

Attempting to avoid addressing the improper legal hurdles placed before Alphapharm, Takeda tries to switch the subject. Takeda transforms each legal error into an unreviewable issue of fact, such as the district court's finding of "teaching away," the examiner's issuance of U.S. Patent No. 4,687,777 ("the '777 patent") despite compound b, and alleged admissions by Alphapharm of "hindsight." But the district court's legal errors infected each of these findings and prevented it from applying this Court's test of obviousness. All obviousness cases are fact-intensive. That reality does not cut off appellate review. Indeed, this Court extensively discussed the facts and analyzed the prior art in reversing the Federal Circuit's determination of nonobviousness in *KSR*. *See KSR*, 127 S. Ct. at 1735-38, 1743-45.

1. There Was No Teaching Away from Compound b

First, Takeda asserts that the prior art specifically "singled out" compound b as a non-starter. (Opp. 29.) This contention is meritless. The prior art taken as a whole taught to the contrary. Years after Sohda II noted the minor side effects of weight gain and brown fat in the highly effective compound b, Takeda declared it to

be "especially" "important" to the Patent Office. (SA24.) Takeda did so to secure allowance of U.S. Patent 4,444,779 ("the '779 patent") that not only covered compound b, but all the ethylated pyridyls Takeda was researching, including pioglitazone. (SA9-19.) While pioglitazone was not specifically disclosed, Takeda drew genus claims to cover all research on ethylated pyridyls. (SA19.) Far from being a "non-starter," Takeda specifically claimed compound b in the '779 patent. (SA19, claim 4.)

Prior art teaches away only when the reference demonstrates that the compound was "'unlikely to be productive of the result sought.'" *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (citation omitted). That could not be true of compound b. Takeda could not have otherwise obtained a claim covering the compound. (SA19.)

2. The Examiner of the '777 Patent Never Saw Takeda's Statements in the '779 Patent

Second, Takeda emphasizes the '777 patent examiner's review of the claimed compounds in light of compound b. (Opp. 7.) But Takeda was careful *not* to put the '779 patent or its file history before the examiner. (RA856-60.) The district court gave Takeda's failure to do so no weight, even though the genus claims of the '779 patent actually covered pioglitazone, and compound b was declared therein to be important. (A111-12.) Any claim that the examiner's issuance supports nonobviousness, is "much diminished" from the clear and convincing standard upon which the Federal Circuit based its affirmance (A27). *KSR*, 127 S. Ct. at 1745.

3. The District Court Erroneously Found and Improperly Weighted "Hindsight" in the Analysis

Finally, Takeda urges that Alphapharm admittedly engaged in "impermissible hindsight." (Opp. 21.) No such admission exists.[2] Rather, Alphapharm determined that the skilled artisan would look carefully at compound b because of its high efficacy and attempt to ameliorate its minor effects by substituting other groups on the pyridyl ring, such as methyl and ethyl. (RA2230, 192:21-22.) Indeed, Alphapharm's expert at trial noted that Takeda taught as much in the '779 patent. (SA112-17.) This too was dismissed as "hindsight" by the district court (A113), and affirmed on appeal.

But hindsight—inevitable in any backward-looking analysis—is not a substitute for the correct obviousness analysis. Rather than focusing on where the prior art might lead the skilled artisan, this Court noted that the obviousness analysis begins with the claims of the invention. *KSR*, 127 S. Ct. at 1742. A reason to combine prior-art elements need only be "apparent" from the prior art after considering any inferences or creative steps that a person of ordinary skill in the art would have employed. *Id.* at 1741. As Takeda admits, hindsight does nothing more than capture "a helpful insight." (Opp. 13.)

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[2] The district court may not have spent the time required to analyze Dr. Rosenberg's testimony comprehensively. The district court confused Alphapharm's Dr. Howard Rosenberg with Mylan's trial expert, Dr. Michael Rosenberg, even drawing an adverse inference against Alphapharm based on that misidentification. (A118, n.64.) The district court admitted its error. (R-JA41, n.1.)

Such an "insight" cannot justify the rigid rule that ensured a finding of nonobviousness on this record, even if it were present. *Id.* at 1740.

II. Takeda Artificially Constricts the "Objective Reach of the Claim" Analysis

Under *KSR*, "neither the particular motivation nor the avowed purpose of the patentee controls" but rather "[w]hat matters is the objective reach of the claim." *Id.* at 1741-42. Takeda interprets "objective" to mean that the purpose of the patentee does not control. (Opp. 16-17.) In doing so, it ignores the remainder of the phrase "reach of the claim." The analysis begins there, not with motivation. Thus, in the very next sentence this Court concluded that obviousness can be shown where "there was an obvious solution encompassed by the patent's claims." *Id.* at 1742.

The Federal Circuit erred by narrowing its analysis, beginning with what might have led the skilled artisan to select the closest prior art, and further to what motivated the skilled artisan to modify that compound in the manner claimed. The analysis should have been much broader, starting with any possible solution conceived by, and within the skill of, the ordinary medicinal chemist that would have led to the invention. (Opp. 8-9.)

III. The Federal Circuit Failed to Apply an "Objective" Analysis as Required Under *KSR*

By focusing on the objective reach of the claim, this Court restored clarity to the law of obviousness. This Court removed unprincipled discretion, and replaced it with an analysis of "objective reach." *Id.* at 1741-42. Objectivity has much to recommend to the law of obviousness, and in particular, the law of structural obviousness because "when a species is patentable over a genus" "is less than clear." (A28, Dyk, J., concurring.)

In *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990), the Federal Circuit announced that for structurally similar compounds a presumption of obviousness arises "where the prior art gives reason or motivation to make the claimed compositions." Motivation to make existed there even though the compounds had different utilities, i.e., tri-orthesters used for "prevent[ing] phase separation between fuel and alcohol" and the claimed tetra-orthoesters used for reducing particulate emissions in fuels. *Id.* at 691. In *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995), the Federal Circuit recognized that if the structure was particularly close, as close as a homolog as here, a prima facie could be made—"a prior art compound may suggest its homologs because homologs often have similar properties." Takeda insists that the language from these cases is discretionary, allowing a court to accept or reject structural obviousness as it sees fit. (Opp. 15.) But on what principled basis? If a prima facie case was made in *Dillon*, it was certainly made on these facts. Greater similarity cannot exist between claims 1 and 5 and compound b. These claims cover a mere homolog. (SA7.)

This Court clarified the law making it easier for the Federal Circuit to bring about uniformity by refocusing the emphasis on the claims, rather than motivation. *KSR*, 127 S. Ct. at 1741-42; *see also Manildra Milling Corp. v. Ogilvie Mills, Inc.*, 76 F.3d 1178, 1181 (Fed. Cir. 1996) (noting that Congress's primary purpose in creating the Federal Circuit was to "bring about uniformity in the area of patent law"). Takeda's constrained interpretation of "objective reach of the claim" would undo much of that work.

IV. The Prior Art Informed the Skilled Artisan about the Expected Properties of the Claimed Compounds

Takeda argues that even where one applies *KSR*'s flexible obviousness analysis, the prior art here gave no "apparent reason" to modify the prior art to obtain the claimed compounds. (Opp. 14.) Takeda is wrong. Applying *KSR* specifically to a case of chemical obviousness, the question is whether the prior art gave the skilled person an apparent reason to make minor modifications to optimize, though not qualitatively change, the utility of the closest prior-art compound. *KSR* asks for an apparent reason to make such closely related compounds, but the reason need not be the same reason that motivated the inventors. *KSR*, 127 S. Ct. at 1741.[3] Nor must the apparent reason to modify active

[3] The district court committed reversible error by holding that the skilled person had to be motivated to "achiev[e] the goals that the inventor sought to accomplish." (A94.) In fact, merely an effective—hypolipidemic and hypoglycemic—compound was enough of a reason under *KSR* for the skilled person to make the very minor changes to the closest prior art to obtain the claimed compounds.

prior-art compounds be explicit. *Id.* (noting that the reason to modify need not "seek out precise teachings directed to the specific subject matter of the challenged claim").

But here Takeda supplied that apparent reason by explicitly telling the world that the very modified compounds that it eventually claimed in the '777 patent would yield useful antidiabetic compounds. (SA11.) Takeda publicly and unequivocally supplied another apparent reason, during prosecution of its earlier '779 patent to antidiabetic TZDs. The '779 patent generically claimed the same compounds that Takeda specifically claimed in the '777 patent, and to obtain the '779 patent Takeda asserted that:

> the substituents in this case, ***actually cover a relatively narrow and well-defined group of constituents.*** Moreover, there should [be] no reason in the instant case for the Examiner to doubt that ***the claimed compounds having the specified substituent would function as a hypolipidemic and hypyglycemic (sic) agent as specified*** in the instant disclosure.

(SA26–27) (emphasis added.) Thus, the skilled person had an express reason to modify the closest prior-art compound. There was definitely a reason—even if not the same as the inventor's purported reason of lowering toxicity—for the skilled person to make the claimed compounds: they would be useful antidiabetic agents. At the very least such modifications—which Takeda candidly insisted were a "narrow and well-defined" group—were obvious to try. Even the district court admitted as much. (A125-26.)

Takeda argues, as a last resort, that even if the prior art gave an apparent reason to modify compound b to obtain pioglitazone (with similar utility), that pioglitazone had unexpected results, and was thus patentable. (Opp. 29.) ***Unexpected results*** may rebut a case of prima facie structural obviousness. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir.), *cert. denied*, 128 S. Ct. 110 (2007). But "[e]xpected beneficial results are evidence of obviousness of a claimed invention, just as unexpected beneficial results are evidence of unobviousness thereof." *In re Gershon*, 372 F.2d 535, 537 (C.C.P.A. 1967). Here, the results—hypolipidemia and hypoglycemia—were expected because Takeda had told everyone that this "narrow and well-defined group" would have such properties. (SA26-27.) And while toxicity for one of the claimed compounds was "improved," (*see infra* Part V) this was merely a matter of degree.[4] Superiority alone is insufficient. *See In re Adamson*, 275 F.2d 952 (C.C.P.A. 1960).

V. The Federal Circuit Precluded Key Evidence Refuting the Alleged Unexpected Results of the Claimed Compounds

Takeda asserts that the finding of unexpected results overcame "any prima facie case of obviousness," "independently support[ed] the judgment," and was "not even challenged by Alphapharm." (Opp. 12.) Takeda's assertion lacks merit. First, the district court denied

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[4] Takeda's citation to *In re Ruschig*, 343 F.2d 965, 978 (C.C.P.A. 1965) is inapposite. The prior-art compound there did not share the toxicity continuum with the claimed compound, as is the case here, but was ***lethal***.

Alphapharm the opportunity to rebut Takeda's alleged showing of unexpected results by excluding key scientific studies Takeda itself conducted. Second, Alphapharm challenged the district court's findings concerning unexpected results. (R-JA2350-55; R-JA2824-26.)

To demonstrate unexpected results, Takeda relied on toxicity tests where pioglitazone demonstrated a smaller increase in heart weight, liver weight, and reduction of red blood cells than compound b. During trial, the district court excluded two studies Alphapharm proffered demonstrating that there were no appreciable differences in toxicity results between pioglitazone and compound b. The first study was a 13-week oral toxicity study that found that pioglitazone caused significant increases in heart weights. (RA1642-731.) The second study, a 4-week study, noted that pioglitazone, and specifically its central and right-hand structures (structures that pioglitazone shared with compound b), increased heart weight. (RA1732-815.)

The evidence of unexpected results for the claims was weak, and therefore insufficient to rebut the prima facie case of obviousness. As discussed above, Judge Dyk noted that Takeda never rebutted the prima facie case concerning the remaining compounds with any such showing. (A28.) There is no bar to finding a secondary consideration wrongly decided by the court below. For example, in *Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005), the patentee claimed that the commercial success of its drug alendronate demonstrated nonobviousness. The Federal Circuit disagreed, and reversed the finding. *Id.* So too in *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371,

1379 (Fed. Cir. 2005), where the patentee relied on the unexpected properties of the claimed anti-inflammatory eye drops, but the Federal Circuit disagreed.

Takeda asserts that Alphapharm's alleged admissions constitute "conclusive evidence" to support its claims of unexpected results. (Opp. 33.) However, these admissions were based on early depositions concerning data provided to the Patent Office. The witnesses were not shown, nor were they apprised of the fact that Takeda later admitted that its presentation of the heart-weight and blood-cell count data concerning compound b and pioglitazone was erroneous. In any event, recognition of "superior" results does not show *unexpected results. In re Merck*, 800 F.2d 1091, 1099 (Fed. Cir. 1986) (noting that the evidence must show that the compounds differ "in such an appreciable degree that the difference was really unexpected.").

Should the Court reverse here with respect to the application of the TSM test, at the very least, the case should be remanded for additional findings on the issue of unexpected results.

CONCLUSION

Alphapharm respectfully requests that this Court grant the petition for a writ of certiorari, vacate the judgment of the Federal Circuit, and if necessary remand to the district court for a complete record on the issue of unexpected results.

Respectfully submitted,

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